Disorder offers clues to aging

Mitochondrial disease may shed new light on energy loss and ailments of later life.

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In retrospect, it was clear from the moment Samantha Fargo was born six years ago that something was very wrong.

At first, she was too weak to breast-feed. By five weeks, she could drink from a bottle, but she had such bad reflux (food backing up the esophagus from the stomach) that her parents, Justine and Bill Fargo of Medford, Mass., had to keep her semi-upright all the time. She didn't walk until she was 1 1/2, and she never had much energy.

For The Record
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It wasn't until she was 4 that Samantha's symptoms gelled into a diagnosis: mitochondrial disease. The often-underdiagnosed genetic problem may shed light on far more common problems, including energy loss with aging and such disorders of later life as Alzheimer's, Parkinson's, diabetes and heart disease.

This spring, she developed gastroparesis, a disorder that caused her stomach and intestines to stop functioning, prompting a long hospitalization. She is now fed via a tube in her stomach and another in a vein.

Conservatively, mitochondrial disease is believed to affect 40,000 to 70,000 Americans, says Christopher Rice, executive director of the United Mitochondrial Disease Foundation.

In reality, the disorders may be "extremely common" and frequently missed by doctors, says Doug Wallace, a mitochondrial DNA geneticist who heads the Center for Molecular and Mitochondrial Medicine at UC Irvine.

The mitochondria are the powerhouses of the cell, little "organelles" -- 1,000 per cell -- that, in the presence of oxygen, convert the energy stored in hydrogen bonds in fat and sugar into the kind of energy the body can use, a substance called adenosine triphosphate, or ATP.

The chemistry is complicated but, essentially, energy is passed through an electron transport chain in and out of five "complexes," or processing areas. At each step, different enzymes come into play. In the final step, an electrical charge glues the components of ATP together.

If the mitochondria don't work properly, the result is a lack of energy and, ultimately, cell death. But mitochondrial disease can be tough to diagnose because lack of energy is a symptom of many diseases. And unlike diseases that attack one main organ, mitochondrial dysfunction can affect multiple organs, especially the brain and muscles.

In some cases, mitochondrial dysfunction is caused by drugs, including the cholesterol-lowering drugs called statins and certain AIDS drugs, says Dr. Bruce Cohen, a neurologist at the Cleveland Clinic Foundation in Ohio.

Over the course of a lifetime, free radicals, destructive oxygen molecules, also damage the mitochondria.

This is a major reason scientists suspect that mitochondrial damage underlies many of the diseases of later life, notes Wallace of UC Irvine. A recent study by Howard Hughes Medical Institute investigators at Yale University found that a decline in mitochondrial function is linked to insulin resistance, a precursor to diabetes.

Perhaps the most dramatic instances of mitochondrial disease are those caused in children by genetic defects. The exact figure is unknown, but mitochondrial disease is believed to occur in one in 2,500 to one in 4,000 births, says Dr. Mark Korson, associate chief of the metabolism service at Boston's Floating Hospital for Children, part of Tufts-New England Medical Center.

There are two ways to inherit it: via defects in the mitochondrial DNA or by defects in genes in the nucleus that act in the mitochondria. The former can be inherited only through defects in the mother's mitochondrial DNA. (Samantha's mother, for instance, has a mild form of the disease.) The latter can come from defects in either parent's nuclear DNA.

The reason for this duality is that the DNA in mitochondria came, about 2 billion years ago, from a bacterium that was engulfed by a cell with a nucleus. Over the eons, some of the mitochondrial genes migrated to the nucleus.

At some point in the cell division cycle, mitochondrial DNA duplicates itself (as DNA in the nucleus also does) and the mitochondria flock to one daughter cell or another.

Within any given cell, some mitochondria may be normal and some sick, a state called heteroplasmy. Depending on how the mitochondria sort themselves out during cell division, some of the new cells may get a lot of bad mitochondria while others do not. This explains why some siblings, even identical twins, can end up with mitochondrial problems of vastly differing severity.

There are no high-tech cures for mitochondrial disease, but anecdotal data suggest that some low-tech remedies, chiefly vitamin supplements, can help.

In theory, one might think that giving people ATP would correct the low-energy problem. Unfortunately, this doesn't work; ATP is such a short-lived molecule that a person would have to consume several times his or her body weight in ATP every day.

A better solution is what doctors call a "mito cocktail," says Dr. Richard Kelley, director of metabolism at the Kennedy Krieger Institute at Johns Hopkins University.

One ingredient of this cocktail is coenzyme Q-10, an enzyme that, in natural form, drives energy production in the mitochondria. Another component is carnitine, which binds to intermediate products in the energy production chain.

Thiamine (vitamin B1) and riboflavin (B12), the antioxidant vitamins C and E, and a supplement called lipoic acid may also help.

At the University of Florida, Dr. Peter Stacpoole, director of the general clinical research center, has been exploring other approaches. One is a drug called DCA (dichloroacetate) that may block the buildup of lactic acid that can occur in mitochondrial disorders. Another, based on the idea that sick mitochondria can't process carbohydrates properly, is a ketogenic or high-fat diet, in which the body, in particular the brain, uses fat instead of carbohydrates for fuel.

Eventually, scientists hope to tinker with what Wallace of UC Irvine calls the mitochondrial "switch" that helps control electrical conductivity in mitochondria.

For the moment, though, except for the "mito cocktails" and common-sense measures like eating a healthful diet, it's a battle for families like the Fargos.

When things flare up, says Samantha's mother, things get "pretty awful. I wish I had more hope that scientists will come up with a cure soon."