**Rare Disease Gets the Spotlight of Discovery**

By T. Anjanette Levert

There are 6,800 rare diseases, reports the Office of Rare Diseases Research (ORDR). The ORDR categorizes a rare disease as one that affects fewer than 200,000 people and estimates 25-30 million people in the United States are afflicted with a rare disease. Sometimes called orphan diseases, rare diseases are frequently due to a mutation in a gene or multiple genes. Some more recognized rare diseases include Cystic Fibrosis, Huntington's Disease and certain types of muscular dystrophies.

Adult Polyglucosan Body Disease (APBD) is a rare disease most people haven’t heard of. It’s a slowly progressive  disorder that affects the nervous system. Most cases of APBD are found in Jewish persons of Ashkenazi (Eastern European) descent, but it is also found in other populations. There are fewer than 300 diagnosed cases worldwide. However, recent findings indicate that this little known disease may be significantly underdiagnosed.

Given the fact that APBD remains unknown to most, increasing awareness is critical. This is being accomplished in part by famed movie photographer and APBD patient Robert Zuckerman, who now finds himself on the other side of the camera. Diagnosed in 2010, he has become a spokesperson for the disease and the APBD Research Foundation (APBDRF).

Persons with APBD inherit recessive mutated genes (one from each parent) that ultimately cause the disorder to be expressed. These genetic mutations initially cause low activity of the body's Glycogen Branching Enzyme (*GBE1)*. *GBE1* is a critical enzyme, as it contributes to making glucose molecules into usable glycogen molecules that provide reserve energy for the body's cells.[[1]](#footnote-2)

Because of the low activity level of *GBE1* in APBD sufferers, they don’t have enough healthy glycogen and much of their glycogen is malformed. The malformed glycogen aggregates into polyglucosan bodies that aren’t optimized to serve as fuel.[[2]](#footnote-3) Instead, they build up, causing damage in the Central Nervous System (nerves in the brain and spinal cord) and the Peripheral Nervous System (nerves in the legs and arms). They also accumulate in skin and muscle tissue. The total accumulation of polyglucosan bodies causes nerve damage and dysfunction throughout the body.

Some of the first symptoms are the loss of feeling in the lower limbs, such as numbness or tingling or weakness in the feet or toes.  This progresses to loss of leg muscle control, often resulting in falls and eventually in an inability to walk. Another early symptom is urinary frequency. Again, muscle control is weakened, and ultimately there’s a progression to loss of bladder control.  A third symptom is extreme fatigue at certain times during the day. This happens because cells needing reserved energy that should be available as stored glycogen have little to call upon. In later stages of the disease, some patients also experience diminished ability to speak, breathe,  swallow, and digest food. Cognitive decline is sometimes found as the disease progresses, as well.

Symptoms often present in persons in their 50s and 60s, when the body can no longer compensate for the nerve damage that has occurred. However, there have been some cases of disease onset in persons in their 30s. Since APBD symptoms are similar to those of Amyotrophic Lateral Sclerosis (ALS, often referred to as "Lou Gehrig's Disease"), Multiple Sclerosis (MS) and prostate hypertrophy ("enlarged prostate" in men), APBD patients often are misdiagnosed. Not uncommonly, they may be prescribed medications that don’t help and may even be encouraged to undergo surgeries that can't improve their symptoms.

Treatment of APBD is generally supportive and addresses symptoms such as lost mobility, incontinence, digestive difficulties, and cognitive impairment. APBD shortens the afflicted person’s life span, with many dying within 10 years of diagnosis. The last few years of life closely follow other degenerative diseases like ALS and MS.

While this disease is currently considered rare, recent evidence suggests it may not be as rare as first believed. A genetic mutation that causes the disease, named “p.Y329S,” was discovered in the 1990s by Dr. Alex Lossos, a physician and researcher at Jerusalem’s Hadassah Medical Center. Thereafter, in August 2012, Dr. Marvin Natowicz, of the Cleveland Clinic, published research in which he concluded, based on a sample of 380 Ashkenazi Jews, that 1 in 34.5 carry the APBD genetic mutation.

Research in the laboratory of Dr. Salvatore DiMauro at Columbia University’s Medical Center, by molecular biologist, H. Orhan Akman, Ph.D and an international group of colleagues, has recently solved the mystery of why a group of patients who, although appearing to have only one mutated gene, have full-blown APBD.[[3]](#footnote-4)  In fact, these patients carry two different mutations. One is the long-known "p.Y329S" mutation that comes from one parent, and the other is a different type of mutation that comes from the second parent. When the two different mutations are present simultaneously, the disease manifests.[[4]](#footnote-5)

Given Dr Akman’s recent findings, which will be published shortly in *JAMA Neurology*, the number of people diagnosed with APBD could increase from a few hundred known cases to thousands. Moreover, Dr. Akman has noted, “Since this (second) mutation is different in nature, there may be some (new) genetic or pharmaceutical treatments that could be used to delay the progress of the disease.” He is now seeking funding to build a new mouse model to investigate this new mutation.[[5]](#footnote-6)

This second mutation requires that researchers and doctors revisit the question of when APBD manifests itself. While APBD is currently considered a neurodegenerative disease that develops in adults, researchers now must examine what happens if a person gets this newly discovered mutation from both parents. One theory is that this combination proves to be fatal prenatally.

The APBDRF has taken on the mission to increase the rate of correct diagnosis of the disease. This means educating the Ashkenazi Jewish population about APBD and also the medical community.  Related to that, the APBDRF is advocating that genetic screening organizations include the two APBD mutations in their panels. A simple saliva or blood test is all that is needed to identify either form of the disease.

Dr. Akman and colleagues are currently testing thousands of medical compounds already in use in the United States, Canada and Europe in an effort to find an effective treatment for APBD. Dr. Akman observes, “Once something goes wrong in the nervous system, it is hard to recover. So if you start the treatments early, the disease may not progress at all.”

Researchers have found several promising compounds. Two of these are cough medicines originally discovered in the 18th century. The short-term efficacy and safety of these compounds relative to APBD are being examined, as well as their long-term effects.

Ultimately, thousands could benefit from clinical trials, among them Robert Zuckerman.

1. Glycogen is the body’s “reserve” fuel and it is stored in cells and activated once normal fuel (free glucose) runs low. The complex glycogen molecule is made up of glucose molecules, some of which form a straight line, while others form off-shoots from the main line, creating side chains. The *GBE1* is involved in the formation of these side chains. The branched structure of glycogen makes it more compact for storage and allows it to break down more easily when it is needed for fuel. The structure is often described as spherical with hydrophilic OH groups on the outside leading to its solubility. This solubility is critical to healthy functioning glycogen.   [↑](#footnote-ref-2)
2. The malformed glycogen is less soluble, so it clumps together and forms polyglucosan bodies. [↑](#footnote-ref-3)
3. In the past, they were identified as manifesting heterozygotes. "Heterozygote" means the person received a mutated gene from one parent while the gene from the other parent appeared normal, They shouldn't have manifested the disease, but they did. [↑](#footnote-ref-4)
4. These individuals are now known as compound heterozygotes because they receive the new mutation discovered by Dr Akman from one parent and the “p.Y329S” mutation from the other parent. [↑](#footnote-ref-5)
5. With money from not only the APBDRF, but also the Muscular Dystrophy Association, Dr. Akman built a “p.Y329S” mouse model a few years ago. [↑](#footnote-ref-6)