Space Life Sciences Research Highlights

Study of Orthostatic Intolerance After Space Flight Leads to Ground-Breaking Discovery of Genetic Defect in Earth-Based Patients

Scientific breakthroughs often are an unexpected bonus from research undertaken with a quite different purpose. So it was for David Robertson, whose experiment on the Neurolab shuttle mission had the objective of finding out why flight crew members, during the initial days after their return to Earth, frequently experienced dizziness, nausea, headaches, and other symptoms whenever they stood up. Robertson did learn more about this temporary orthostatic intolerance—but in the course of his work, he also became the first person to link a genetic defect to the Earth-bound form of the condition.

Imagine hunting for a missing piece to a puzzle—and finding a diamond right beside it. That was, in effect, the outcome of a Neurolab experiment designed to study transient orthostatic intolerance—a readjustment problem for space flight crew members returning to Earth. The Neurolab experiment was successful in ways that the researchers could not have anticipated when they designed their study, because data from earlier studies had led them to expect different results.

Orthostatic intolerance is a problem that occurs in some people when they move from a sitting or lying position to standing upright. The term derives from the Greek words *orthos* meaning "straight" and *statikos* meaning "causing to stand." This simple change in posture—a movement we perform without thinking—puts tremendous stress on the cardiovascular system, which has to make sure that the brain continues to receive sufficient blood despite the sudden pull of gravity on the blood in the abdomen and legs. To prevent fainting or other symptoms that would result from a reduction of blood flow to the brain, the person's blood pressure, pulse rate, and other critical functions have to readjust almost instantaneously.

The autonomic nervous system is largely responsible for making these on-the-fly adjustments. Orthostatic intolerance is the most common autonomic system dysfunction, affecting some 500,000 Americans. Many of those who experience orthostatic intolerance are women, and most are young and otherwise healthy. They are significantly disabled, however, by the palpitations, fatigue, altered mental state, nausea, headache, dizziness, or fainting that occur when they stand up.

A short-term orthostatic intolerance can also occur after severe debilitating illnesses, substantial weight

When astronaut Catherine G. Coleman returns to Earth following her space flight, she may experience the symptoms of orthostatic intolerance when she stands up, as many astronauts do. Here she is exercising on the bicycle ergometer during the STS-73 mission.

loss, prolonged bed rest, or space flight. Up to 64 percent of space flight crew members experience this temporary condition, which typically lasts for 1-5 days following their return to Earth.

To understand how spending time in microgravity might bring about this autonomic dysfunction, Dr. David Robertson of Vanderbilt University and his colleagues designed a comprehensive experiment for the Neurolab space shuttle mission that flew in April 1998. The investigators used sophisticated techniques to measure physiologic and biochemical signs of autonomic activity in four crew members before, during, and after the flight. The levels of the neurotransmitters norepinephrine and epinepherine were measured in the blood under various conditions (neurotransmitters are chemicals that permit nerve impulses to pass from nerve cell to nerve cell). Studies of activity of the sympathetic nervous system (a component of the autonomic system) examined responses to various types of voluntary and involuntary muscle movements. Tracer doses of radiographically tagged norepinephrine were administered to track the reasons for any norepinephrine anomalies.

"The Neurolab experiments were very successful for us, because we were able to collect all the data we were hoping for, including the technically difficult measurements of sympathetic nerve activity during the flight," said Dr. Robertson.

The results of the Neurolab's comprehensive studies contradicted what the researchers expected to find based on earlier bed rest and inflight studies. Many of the earlier flight experiments had been hampered by the difficulties of measuring neurotransmitter activity in the space flight environment. Instead of seeing reduced sympathetic nervous system activity, which they had hypothesized would occur due to the changed demands on the body in the microgravity environment, they found increased sympathetic nervous system activity, as evidenced by high levels of norepinephrine and muscle sympathetic nerve activity. "The increase was consistent with our studies of some Earth-bound patients with orthostatic intolerance," said Dr. Robertson.

The findings sent the investigator back to the data from Earth-based patients, to see whether the reasons for high levels of norepinephrine were the same in flight and on Earth. "There can be a number of reasons why norepinephrine levels might be elevated," Dr. Robertson said. "In the flight crew, for example, we found that these levels were elevated because the nerve cells were releasing high levels of the chemical. But there are other possible explanations. For example, there can be failure of the transporter system that moves chemicals like norepinephrine into and out of cells and hence failure of the systems that remove norepinephrine from the blood."

Clearance of norepinephrine was precisely the problem in a 33-year-old woman with orthostatic intolerance. Noting that the woman's identical twin also experienced symptoms of orthostatic intolerance, Dr. Robertson and his colleagues conducted studies of norepinephrine responses to stressors in both sisters, their mother, seven other siblings, and in ten matched but unrelated control subjects without orthostatic intolerance. The results suggested that the problem was with the norepinephrine transporter. The presence of the same findings in both twins suggested a genetic defect.

Using DNA samples collected from the twins, their siblings, and their mother, and matching these with DNA from 254 unrelated individuals, Robertson's team sequenced the gene and found the defect—the first time a specific functional abnormality has been linked to a genetic defect in a monoamine transporter in humans (norepinephrine is a monoamine), and the first time a genetic link has been found in any form of orthostatic intolerance. While this finding does not explain all cases of orthostatic intolerance, it has shifted attention to a previously unexplained mechanism of a very common clinical problem.

Future experiments in space will test whether specific medications to control the release of norepinephrine can alleviate or eliminate post-flight orthostatic intolerance. As for Dr. Robertson's discoveries about the genetically linked form of Earth-bound orthostatic intolerance, they have already found a place in the annals of medical science. "Diagnosis and therapy for patients like these will most definitely be affected," said Dr. Robertson. "Clearance and release of norepinephrine are two different issues with two different potential therapies."

References

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