Spinal muscular atrophy may also affect the heart

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Along with skeletal muscles, it may be important to monitor heart function in patients with spinal muscular atrophy (SMA). These are the findings from a study conducted by Nationwide Children's Hospital and published online ahead of print in *Human Molecular Genetics*. This is the first study to report cardiac dysfunction in mouse models of SMA.

SMA is a debilitating neurological disease that leads to wasting away of muscles throughout the body. Historically, scientists and physicians believed that SMA only affected skeletal muscles; however, new data suggests that this genetic disease may also impact the heart.

"A few studies regarding SMA patients have implicated the involvement of the cardiovascular and the autonomic nervous system," said the study's co-author Brian Kaspar, PhD, principal investigator in the Center for Gene Therapy at The Research Institute at Nationwide Children's Hospital. "However, there have been few to no highly powered and controlled studies to determine how common these cardiovascular anomalies are in these patients."

The reports of altered blood flow and slowed heart rate in some SMA patients prompted Kaspar's team to examine whether a cardiac deficit is present in a mouse model of severe SMA, developed by Arthur Burghes, PhD, professor of Molecular and Cellular Biochemistry at The Ohio State University College of Medicine, which is routinely used for drug and therapeutic-based screening.

They analyzed heart structure of the SMA mice compared with normal mice, and found that there were significant structural changes occurring in the heart of the SMA mice, along with severely impaired left-ventricular function. SMA mice also had significantly lower heart rates. After examining the underlying structure of the mouse heart cells they found it similar to the cellular structure of a heart biopsy from patient with type 3 SMA.

Kaspar's team recently developed a gene therapy approach shown to successfully deliver the missing SMN protein to SMA mice and improve neuromuscular function. Next, the team studied whether the discovered heart defects could be corrected by this gene delivery treatment. Results showed that restoring SMN levels completely restored heart rates and prevented the early development of dilated cardiomyopathy.

Pam Lucchesi, PhD, director of the Center for Cardiovascular and Pulmonary Research at The Research Institute at Nationwide Children's Hospital and study co-author, says it is still not clear which mechanisms are fully responsible for the heart deficits seen in the SMA mice, but data suggests that neuronal, autonomic and developmental components all may play a role.

"Our gene delivery strategy has unique advantages in that it targets neurons within the central and peripheral nervous system as well as the cardiac tissues," said Lucchesi, also a faculty member at The Ohio State University College of Medicine.

More research is needed to determine whether the cardiac deficits are unique to the mouse or whether SMA patient of various severities have or will develop similar issues. Still, Kaspar, also on the faculty at The Ohio State University College of Medicine, says clinicians should be acutely aware of potential heart dysfunction in a subset of SMA patients.

"Increasing reports of autonomic dysfunction together with our current findings warrant increased attention to the cardiac status of SMA patients, and potentially highlights the need to investigate cardiac interventions alongside neuromuscular treatments," said Kaspar.

Provided by Nationwide Children's Hospital