PNAS: Heart defects identified in progeria patients that increase the risk of arrhythmias and premature death

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La información permitirá abrir nuevas líneas de investigación para el desarrollo de nuevas terapias dirigidas a corregir estos defectos que caracterizan a la progeria

Researchers at the *Centro Nacional de Investigaciones Cardiovasculares Carlos III* (CNIC), working in collaboration with colleagues at other centers in Spain and abroad, have identified defects in the hearts of progeria patients that appear to be related to an elevated risk of arrhythmias and premature death. The study, published *The Proceedings of the National Academy of Sciences* (*PNAS*), shows that these risks are linked to anomalies in the transmission of electrical signals in the hearts of individuals with Hutchinson-Gilford progeria syndrome (HGPS), also known as progeria. Similar findings were observed in a mouse model of this disease studied by the research team. The findings of this study open the way to research into the development of new treatments to correct these characteristic defects associated with progeria. The study could also provide clues about the mechanisms involved in the development of cardiovascular disease during normal aging.

Progeria is a very rare genetic disease, estimated to affect fewer than 400 people worldwide. The disease is caused by a mutation in the gene encoding laminin A (LMNA). “The mutation causes an incorrect processing the messenger RNA encoded by the gene, and this results in the production of

an anomalous version of the pre-laminin A protein called progerin, which accumulates in the cell nucleus," explains study coordinator Dr. Vicente Andrés. Children presenting progeria symptoms can be diagnosed with a genetic test, but as yet there is no effective treatment for the disease, and patients die in the first two decades of life. The cause of death in progeria is principally related to cardiovascular problems, but according to first author Dr. José Rivera-Torres "there is a great void of knowledge about the mechanism responsible for the anomalies that characterize progeria."

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The *PNAS* study shows for the first time that HGPS patients share similar defects with mice lacking the metaloproteinase ZMPSTE24/FACE1, which the team uses as an experimental model of progeria. The patients and mice both progressively develop electrocardiogram anomalies. "The conduction anomalies in the hearts of progeric mice are accompanied by altered expression of the protein connexin 43, and similar alterations are seen in the hearts of HGPS patients," comments Dr. Andrés. Normally, connexin 43 accumulates at gap junctions—structures in the cell membrane that are essential for the correct propagation of electrical impulses from one cardiomyocyte to another. Altered connexin 43 expression is found in many cardiovascular diseases affecting the general population, and is also associated with normal aging. Aberrant connexin 43 expression provokes electrical alterations in the myocardium that favor the development of arrhythmias. The *PNAS* study shows that in the cardiomyocytes of progeria patients and progeric mice, connexin 43 is incorrectly localized laterally and accumulates in the perinuclear region of the cytoplasm.

New therapies

According to coauthors Drs. José Jalife and David Filgueiras, "these findings open a new chapter in the understanding of the cardiovascular consequences of this disease." For example, the similarities between patients and the mouse model of HGPS suggest that mislocalization of connexin 43 reduces connectivity between cardiomyocytes, thus increasing the risk of arrhythmias and premature death. "To build on these findings, we are now studying why connexin 43 mislocalizes in the hearts of HGPS patients and progeric mice. These studies could also help in the design of therapies to correct the cardiac electrical defects in progeria," says Dr. Andrés.

Many of the anomalies of progeria are also characteristics of normal aging, suggesting that shared mechanisms trigger cardiovascular alterations in HGPS patients and the elderly population. Dr. Rivera-Torres comments that, consistent with this idea, other studies have demonstrated the production of prelaminin A and progerin in cells and tissues of individuals unaffected by HGPS. The research team therefore hopes that the study of this rare disease will provide important information about the mechanisms implicated in normal aging and associated heart disease.

"Cardiac electrical defects in progeroid mice and Hutchinson–Gilford progeria syndrome patients with nuclear lamina alterations". http://www.pnas.org/cgi/doi/10.1073/pnas.1603754113

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