Genetic heart diseases may be responsible for unexplained stillbirths

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Genetic researchers have made an important step towards resolving the mystery of the causes of intrauterine fetal demise (IUFD), or stillbirth, where a baby dies in the womb after the 14th week of gestation. IUFD is responsible for 60% of perinatal mortality and occurs in about one in every two hundred pregnancies in Europe. Up to half of these stillbirths are unexplained. Now scientists from Italy, Germany, and the US have found that up to 8% of these unexplained deaths may be caused by specific genetic heart conditions.

Research group from the University of Pavia, Italy shows for the first time that cardiac channelopathies, hereditary diseases in which the heartbeat rhythm is disturbed, were likely to have played a causative role in some IUFD deaths . "Since we knew that 10-15% of sudden infant death syndrome cases carry genetic variants associated with long QT syndrome or Brugada syndrome, we decided to investigate whether sudden death due to malignant arrhythmias could underlie some cases of IUFD as well", Ms Alice Ghidoni, a PhD student, explains.

The researchers carried out molecular screening of stillborn fetuses where the cause of death remained unexplained after extensive post-mortem investigation. Informed consent was obtained from the parents. They looked for mutations of three genes, two of them involved in long QT and one in both long QT and Brugada syndromes, and found three disease-causing variants that were present in the IUFD cases, but absent in more than 1000 ethnically-matched controls.

Genetic testing is still quite rare in IUFD, but it is an important tool for uncovering the causes of unexplained death, says Ms Ghidoni. "The most common causes of fetal death are chromosomal abnormalities, infections, fetal-maternal haemorrhages, and maternal diseases", she says. "Most of these are relatively easy to identify. Since genetic screening is a long, expensive and complicated procedure, currently it is not routinely performed in cases where an autopsy has not shown the cause of death. However, such molecular investigation could be very useful to identify specific genetic defects occurring in the family, so that future pregnancies can be monitored with close clinical follow-up. In some cases, life-saving treatment could be given."

Identification of a fetus with a gene mutation for a cardiac channelopathy allows for treatment for the mother with drugs such as beta-blockers, the same treatment that is given to adults who have been identified with long QT syndrome.

Because the research was carried out by scientists from a number of different centres and countries, it was not possible to systematically collect parental DNA. However, as part of the planned expansion of the investigation, the researchers now intend to enlarge the study population further and to collect DNA from all family members. Cardiac channelopathies run in families, so genetic testing will be able to identify not just those parents who are at risk of an affected pregnancy, but also all family members who may be unaware that they have a potentially fatal heart condition.

"We have also identified new candidate genes which may be linked to cardiac channelopathies, and we will investigate them in our follow-up work", says Ms Ghidoni. "Our current work shows that nearly 3% of IUFDs may be caused by a genetic variant with a cardiac disease-causing role, and another 5% by a variant that may predispose to disease. We believe that the new candidate genes may enlarge this field yet further.

This is vitally important because we can then depict a clear picture of arrhythmic risk in perinatal life, both before and after birth.

"We believe that it is very important to increase knowledge of these genetic disorders among paediatric cardiologists and gynaecologists and that genetic testing should be included in post-mortem analysis. Many more lives can be saved if there is sufficient awareness of these devastating conditions among healthcare professionals, as well as among the affected families who in many cases have already suffered enough," Ms Ghidoni will conclude.

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