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Kilby, Mark

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EDITORIAL

Nonimmune Hydrops Fetalis — More Than Meets the Eye?

Mark D. Kilby, D.Sc., M.D.

Nonimmune hydrops fetalis (NIHF) has a striking appearance on ultrasonography and is classically defined by the presence of pathologic fluid accumulation in at least two fetal sites, including the serous cavities (pericardial, pleural, and peritoneal), with associated skin edema. Its diagnosis is established by first ruling out maternal red-cell alloimmunization. NIHF occurs in up to 1 in 1700 fetuses and has multiple causes: chromosomal abnormalities, structural malformations (especially cardiac and thoracic), inborn errors of metabolism, and in utero infections.[1] The phenotype is usually distinct, but recently, increased nuchal translucency and cystic hygroma during the first trimester have been added to the diagnostic criteria.[2] Among women with fetuses that have these features during the first trimester, perinatal mortality is particularly high, and very thick nuchal translucency (i.e., exceeding 5 mm), cystic hygroma, and suspected lymphatic-related hydrops fetalis are all associated with pathogenic genetic variants that portend a poor outcome.[2,3] Exome sequencing is a method that yields the DNA sequence of most of the protein-coding genome and presents unique opportunities and challenges for invasive prenatal genetic testing.[4] In two prospective studies in which exome sequencing was used to evaluate fetal structural anomalies, diagnostic variants were identified in 9% and 24% of fetuses with NIHF.[5,6]

In an article now published in the *Journal*, Sparks and colleagues[7] report their evaluation of a case series of 127 consecutive fetuses with NIHF that were defined as such according to the nonstandard definition of one or more pathologic fluid collections and in which the NIHF remained unexplained after either fetal karyotype analysis or chromosomal microarray analysis. Cases in which alloimmunization, congenital viral infection, or twin-to-twin transfusion syndrome were present had been excluded. Plausible pathogenic variants identified by exome sequencing were reviewed by a multidisciplinary team to determine whether a genetic diagnosis could be established. The phenotypes of the fetuses in the study were heterogeneous; there was an increased thickness of nuchal translucency (≥3.5 mm) or a cystic hygroma during the first trimester in 23% of the cases, evidence on ultrasonography of an isolated single effusion in 17%, and at least two abnormal fetal fluid collections in 61%. The fetuses may or may not have had concurrent structural anomalies.

Exome sequencing identified pathogenic variants, which were associated with a range of prognoses, in 29% (37 of 127) of the fetuses with the use of a tiered method of interpretation.[6] Women who were currently pregnant or who had had a live birth received their results within 14 to 28 days after samples were received at the laboratory; in cases of prenatal testing, such rapid turnaround times are crucial. Among the cases with a diagnostic variant identified, live birth occurred in only 14% (a result that was consistent with the known high fetal mortality associated with NIHF), and postnatal death occurred in 19% (which was not substantially different from the percentage of postnatal deaths among the cases in which variants were not identified). The most common genetic causes of NIHF were variants that resulted in disorders affecting the RAS–MAPK cell-signaling pathway (known as RASopathies) (30% of the cases); among these cases, 64% had a variant that caused the Noonan syndrome. In addition, vari-

ants were classified as causing inborn errors of metabolism (11% of cases), musculoskeletal disorders (11%), and lymphatic, neurodevelopmental, cardiovascular, and hemorrhagic disorders (8% each). Most of the cases with diagnostic variants (68%) were autosomal dominant; of these cases, 88% were de novo (i.e., the variant was not present in the germline of either biologic parent). Among the cases with genetic diagnoses, 27% of the variants were autosomal recessive (95% of which were inherited), and 1 case with a diagnostic variant had an inherited X-linked recessive disease. Parental consanguinity was noted in only 3% of the fetuses analyzed, and none of these fetuses had pathogenic variants.

Increased nuchal translucency is an important "biomarker" seen on ultrasonography that is associated with an increased risk of fetal structural anomalies and a wide range of genetic causes, but if these are ruled out, this condition may have a good prognosis.[8,9] In such cases, abnormalities of the thoracic lymphatic and venous systems may be present, and more complex phenotypes may develop with advancing gestation.[3] Among the cases in this series with increased nuchal translucency or cystic hygroma (either isolated or concurrent with other anomalies), 31% had an identified pathogenic diagnostic variant; however, when the analysis was restricted to cases with isolated nuchal translucency or cystic hygroma, the yield was relatively low (7%). This finding is consistent with that of another case series (24 fetuses), in which only fetuses with very thick nuchal translucency and other structural anomalies were associated with identification of pathologic variants.[10]

These observations support the likelihood of identifying a diagnostic variant in fetuses with increased nuchal translucency or cystic hygroma in combination with other fluid collections or anomalies, as well as in those with two or more abnormal fluid collections. However, the diagnostic yield for isolated increased nuchal translucency or cystic hygroma appears to be low.

The results of this relatively large case series indicate that NIHF is a fetal phenotype that should be considered for prenatal exome sequencing to identify genetic disease associated with additional complications. The highest diagnostic yields are obtained when concurrent structural anomalies (including cystic hygroma) are identified. It reinforces the importance of early multidisciplinary selection of phenotype and detailed variant interpretation in combination with the assessment of fetal ultrasonographic findings. Sparks et al. achieved a high diagnostic yield by uploading sequencing data together with detailed phenotypic data (with the use of a standardized vocabulary of phenotype abnormalities) into a software package that prioritizes candidate variants within a bioinformatic pathway (whereby American College of Medical Genetics and Genomics criteria are used to prioritize variants according to their likelihood of being pathogenic). This process enabled timely feedback about pathogenic variants to parents. The data from this study illustrate the usefulness of prenatal exome sequencing to prospectively identify serious genetic disease in cases of NIHF with additional serous effusions, with or without increased nuchal translucency or cystic hygroma.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the College of Medical and Dental Sciences, University of Birmingham, and the Fetal Medicine Centre, Birmingham Women's and Children's Foundation NHS Trust, Birmingham, United Kingdom.

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