Lysosomal storage disease as an etiology of nonimmune hydrops

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We performed a systematic review of the literature to evaluate the incidence and types of lysosomal storage disorders (LSDs) in case series of nonimmune hydrops (NIH). PubMed and Ovid were reviewed for case series evaluating the workup of NIH diagnosed in utero or in the neonatal period in human subjects. Search terms were as follows: nonimmune hydrops, non immune hydrops, metabolic genetic disorders, and lysosomal storage disorders. The time period searched was 1979 through January 2014. Retrospective case series with at least 5 cases of fetal and/or neonatal NIH with its workup mentioned were identified. Idiopathic NIH was defined as NIH without an apparent cause after an initial workup. Exclusion criteria included studies published in languages other than English and review articles. The 3 authors screened all abstracts and manuscripts independently. Metaanalysis of Observational Studies in Epidemiology guidelines were followed. Fifty-four case series with 678 total cases of NIH were identified. The overall incidence of LSD was 5.2% (35 of 678) in all NIH cases that tested for any LSD and 17.4% (35 of 201) in idiopathic NIH cases. The 3 most common LSDs identified in cases of NIH, in order of decreasing incidence, were Mucopolysaccharidosis type VII, Gaucher's disease, and GM1-gangliosidosis. LSDs occur in 5.2% of all NIH cases and in 17.4% of idiopathic NIH cases and so should be screened for in this clinical scenario. Additionally, if a comprehensive LSD workup is completed on idiopathic cases, 29.6% of those would be reclassified as LSD. LSD testing does not only allow diagnosis but also ensures better counseling, appropriate management, and planning for possible early intervention. Moreover, their detection may aid in a prenatal diagnosis in subsequent pregnancies.

Key words: lysosomal storage disease, nonimmune hydrops, systematic review

Hydrops fetalis is a life-threatening fetal state that is defined by the pathologically increased fluid accumulation in fetal soft tissues and body cavities. Specifically, hydrops fetalis is diagnosed by the presence of 2 or more abnormal fluid collections in the fetus including ascites, pleural effusions, pericardial effusions, and skin edema.[1] This condition is diagnosed by prenatal ultrasound. A subset of hydrops fetalis that is classified as nonimmune hydrops fetalis (NIH) is comprised of cases that are not caused by red blood cell alloimmunization. NIH accounts for almost 90% of cases of hydrops, [2] with an incidence of 1 in 1700-3000 pregnancies. [3,4]

NIH is the end-stage manifestation of several disorders. The differential diagnosis is extensive (Table 1), and the success in identifying a cause depends on the extent of the workup.[1] Table 2 represents an example of a basic pre- and postnatal workup for NIH.[1] Although older studies report many cases as idiopathic,[5-7] recent larger series and a recent systematic review report that a cause can be found in up to 85% of cases.[8] Some of the most common causes of NIH are cardiac disorders (both structural malformations and arrhythmias), other structural malformations, chromosomal anomalies, infections, and hematological abnormalities.[1]

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Materials and methods

Lysosomal storage disorders (LSDs) have been reported to account for about 1-15% of the causes of NIH cases,[4,9-11] yet in clinical practice, these LSDs are often not evaluated. Our objective was to evaluate, by review of the literature, the significance of LSDs as the underlying etiology of NIH and whether evaluating for LSDs would be clinically useful in the workup of NIH.

Methods for review

PubMed and Ovid were reviewed for case series evaluating the workup of NIH diagnosed in utero or in the neonatal period in human subjects. Search terms were as follows: nonimmune hydrops, non immune hydrops, metabolic genetic disorders, and lysosomal storage disorders. The time period searched was 1979 through January 2014. Exclusion criteria were studies published in languages other than English, abstracts, unpublished studies, and review articles. Hand searching was also done using reference lists of obtained articles. The literature search was done by 2 investigators (A.C.G. and V.B.).

Retrospective studies and case series with cases of NIH with its workup described were identified. We included manuscripts with at least 5 cases of NIH to minimize publication bias. The criteria for the diagnosis of NIH were recorded. Three reviewers (A.C.G., V.B., and P.L.) screened all abstracts and manuscripts independently. Articles were

TABLE 1
List of most commonly reported causes of NIH

Conditions associated with NIH	Approximate percentage of NIH associated with condition
Cardiovascular	30%
Fetal arrhythmias	
Structural	
Cardiac/thoracic mass	
High cardiac output failure	
Vascular disorders	
Extracardiac anomalies	20%
Thorax	
Urinary	
Gastrointestinal	
Skeletal dysplasias	
Chromosomal abnormalities	20%
45x (or mosaic 45X/46XX) trisomy 21, trisomy 18, trisomy 13, triploidy	
Infections	10%
Hematologic	5-10%
Red cells loss	
Underproduction	
Monochorionic twin pregnancy	5%
Metabolic/genetic syndromes	2-6%

NIH, nonimmune hydrops.
Adapted, with permission, from Berghella et al.[1]

Gimovsky. Systematic review of LSD in NIH. Am J Obstet Gynecol 2015.

screened for comparability of cases, and large studies were reviewed for overlapping cases. References for included articles are provided in the Reference section, and references excluded from the article are available from the authors upon request.

In each article reporting the workup of NIH, the details of the workup (eg, ultrasound, karyotype, etc) were recorded, including any metabolic tests, such as LSD. Pre- vs postnatal workups were recorded. If no diagnosis was identified as the probable cause for the NIH after the initial workup, the case was defined as idiopathic.

Each case series with 5 or more cases of NIH was evaluated for testing for LSD. LSD was defined as a category of metabolic disorders caused by defects in the lysosomal function, resulting in the accumulation of undegraded materials that triggers a cascade of pathological outcomes.[12] The Methods section of each article was evaluated to see which LSDs were screened and how many of the cases of NIH received this LSD screening (Table 3). Only cases of LSD confirmed by enzymatic or genetic tests were included. Which LSDs were the most commonly tested for was evaluated.

Our primary outcome was the incidence of any LSD in the studies of NIH in which LSDs were tested. The Meta-analysis of Observational Studies in Epidemiology guidelines were followed for systematic review of observational studies.[13] This study was exempt from institutional review board approval.

Results

The Figure reports the data extraction. Of the 54 case series reporting a workup for NIH, 15 (27.8%) reported testing for LSD.[9,10,14-26] In these 15 series, a diagnosis as probable etiology for NIH was detected in 512 of 678 cases (75.5%) (Tables 3 and 4). One study[27] reported genetic diagnoses but did not define what was included in that category. Another series[28] had 10 cases of LSDs, but not all were NIH and we were unable to find out which cases were associated with NIH and which ones were not correlated.

In comparison, in the other 39 series without an LSD workup, a diagnosis was achieved in 2028 of 2464 cases (82.3%).

In the 15 series of NIH in which the LSD workup was done, the diagnosis of NIH was often made using slightly different criteria (Table 3). The initial workup for NIH differed in each study, and for some studies the initial workup was not described. In the workup for LSD, most studies (10 of 15, 67%) did not mention specific tests that were ordered, whereas others (5 of 15, 33%) did provide the exact tests for which LSDs were tested (Table 3). It is unclear whether LSD testing was completed in all cases within the series.

We cannot report on the average number of LSDs tested per study because many are not listed. The majority of studies in which LSDs were tested had their workup for NIH done both pre- and postnatally (53%). Three studies made the diagnosis prenatally, 5 studies made postnatal diagnoses, and 7 studies used a combination of both methods. Of the postnatally diagnosed cases, many were diagnosed only after delivery.

Table 4 shows the results of positive LSDs that were diagnosed from the 15 studies that tested for LSDs. Of the 678 total NIH cases identified, 477 (70.3%) had a diagnosis other than LSD, 166 (24.5%) were idiopathic, and 35 (5.2%) were diagnosed with LSD