

## Disparate Clinical Presentation of Neonatal Hemochromatosis in Twins

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**ABSTRACT.** Neonatal hemochromatosis (NH) is a rare disease of gestation that results in fetal liver injury and extrahepatic siderosis. The etiology of NH is not fully understood. However, the rate of recurrence of NH in the pregnancy after an affected one is ~80%. A spectrum of liver disease has been recognized, spanning from liver failure in the fetus or neonate to infants that survive with medical therapy. Here we report on 2 sets of fraternal twins, each set with a gross disparity in the severity of presentation: 1 infant with liver failure and the other nearly unaffected. These findings suggest a need to look carefully for subclinical disease in the siblings of patients with NH by using sensitive tests such as those for ferritin and  $\alpha$ -fetoprotein. They also suggest that affected infants may be missed when using routine clinical testing, which would lead to the apparent rate of recurrence, understating the actual recurrence rate. *Pediatrics* 2005; 116:e880–e884. URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2005-0784](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-0784); neonatal hemochromatosis,  $\alpha$ -fetoprotein, ferritin, neonatal liver failure.

ABBREVIATIONS. NH, neonatal hemochromatosis; INR, international normalized ratio; AFP,  $\alpha$ -fetoprotein.

Neonatal hemochromatosis (NH) is a rare disorder that affects the fetus in late gestation and usually results in severe liver injury and hepatic siderosis.<sup>1</sup> The diagnosis is established by demonstrating siderosis of extrahepatic tissues, most prominently epithelia of the exocrine pancreas, thyroid follicles, and oral mucosal (“minor salivary”) glands.<sup>2–4</sup> The mechanisms of liver injury and diffuse siderosis are not fully understood.

NH usually causes severe fetal injury and often fetal loss. Severe intrauterine growth restriction and oligohydramnios are observed in nearly all cases. Cases of NH with renal tubular dysplasia are thought to be the consequence of loss of critical liver function necessary for renal maturation to occur and date the onset of liver failure to ~24 weeks’ gestation.<sup>5,6</sup> The characteristic clinical presentation in live-born infants includes severe perinatal distress, hypoglycemia, and liver failure manifest within hours of birth. However, a spectrum of illness has been recognized, with some well-documented cases showing

lesser liver injury.<sup>7,8</sup> The cause of this “incomplete penetrance” of a usually lethal condition is unknown. Also the incidence of infants with NH that is undetected because of the lack of clinical illness is not known.

NH has an unusual pattern of recurrence that cannot be explained easily by genetic inheritance.<sup>3,9</sup> A woman may have unaffected offspring before having the first child with NH, after which the rate of recurrence is as high as 80%. This pattern has suggested to us that NH is an alloimmune disease.<sup>10</sup> However, there are documented families wherein unaffected siblings follow the index case or alternate with affected infants and 1 set of triplets with 1 affected and 2 unaffected infants.<sup>9</sup> There are several instances of maternal half-siblings being affected but not of paternal half-siblings.<sup>8,11,12</sup> Counseling related to future childbearing has been based on making a firm diagnosis in the index case and the assumption of a high recurrence rate.<sup>13,14</sup> At present, there is no test to determine if a pregnancy will be affected, and there is no effective approach to prenatal diagnosis.

We report 2 sets of fraternal twins with NH; in each set, 1 infant expressed liver failure and the other was nearly unaffected. These cases further highlight the spectrum of disease severity in NH and emphasize the importance of performing sensitive laboratory investigations in “apparently healthy” newborn siblings of infants with NH.

## CASE REPORTS

## Twin Set 1

These were fraternal twins conceived by in vitro fertilization and born at 35 weeks of gestation to unrelated parents. The mother was 30 years old and gravida 1, para 0. Spontaneous preterm labor at 35 weeks was accompanied by mild preeclampsia.

Twin A was male, had a nuchal cord, and had Apgar scores of 3 at 1 minute, 7 at 5 minutes, and 9 at 10 minutes. He required intubation at birth and received intratracheal surfactant before extubation on the first day of life. His weight was appropriate for his gestational age. Clinically, he was reported to be jaundiced and mildly edematous with no palpably enlarged liver or spleen. His initial arterial blood gas showed a pH of 7.17 with a metabolic acidosis (base deficit: –13.8 mmol/L). Additional evaluation demonstrated failure of liver synthetic function (Table 1). An abdominal ultrasound showed a small liver with patent vessels, an open ductus venosus, and ascites. He was treated with antibiotics, intravenous dextrose infusion, and fresh frozen plasma infusions with little improvement and was transferred to Children’s Memorial Hospital at 16 days of life. He was jaundiced and had generalized edema, tense ascites, and hepatosplenomegaly. Additional test results of interest were: urea, 3 mg/dL (normal: 5.0–15 mg/dL); creatinine, 0.2 mg/dL (normal: 0.3–0.5 mg/dL); venous ammonia, 101  $\mu$ mol/L (normal: 21–50  $\mu$ mol/L); lactate, 1.5 mEq/L (normal: 0.5–2.2 mEq/L); and uric acid, 1.9 mg/dL (normal: 2.0–7.0 mg/dL). Normal or nondiagnostic plasma acylcarnitine profile, erythrocyte galactose-1-phosphate uridylyl transferase level,

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Accepted for publication Jun 13, 2005.

doi:10.1542/peds.2005-0784

No conflict of interest declared.

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**TABLE 1.** Representative Test Results in Twins With NH Near the Time of Presentation as Newborns and at the Most Recent Follow-up

	Normal Newborn Values	Twin Set 1				Twin Set 2			
		Twin A		Twin B		Twin A		Twin B	
		Newborn	1 y	Newborn	1 y	Newborn	10 mo	Newborn	10 mo
<b>Bilirubin</b>									
Total, mg/dL	<7.0	13.5	0.5	3.9	0.5	5.3	0.3	6.0	0.2
Direct, mg/dL	<0.3	6.6	0.1	0.5	0.2	0.4	—	1.0	—
Alanine aminotransferase, IU/L	<52	27	55	41	35	21	18	38	24
Albumin, g/dL	2.0–3.7	1.1	—	2.9	—	1.8	—	1.5	—
INR	0.8–1.8	4.7	1.1	1.0	1.0	2.2	0.9	3.4	1.0
Fibrinogen, mg/dL	50–140	<40	—	—	—	111	—	35	—
Ferritin, ng/mL	22–322	1161	49	685	38	1674	—	3945	—
AFP, ng/mL	<20 000*	34 085	31	217 060	50	298 948	68	294 047	202

— indicates that the tests were not performed.

\* The accepted abnormal value for serum AFP for term neonates is >84 000 ng/mL and for 32 weeks of gestation is >200 000 ng/mL.

urine-reducing substances, urine succinylacetone, urine organic acids, and plasma amino acids excluded most inborn errors of metabolism. Mass spectroscopy of urinary bile acids excluded an inborn error of bile-acid synthesis. Appropriate tests looking for rubella, cytomegalovirus, toxoplasma, and herpes simplex were negative. MRI (Fig 1A) demonstrated excess iron in liver, pancreas, heart, and adrenal glands.<sup>15</sup>

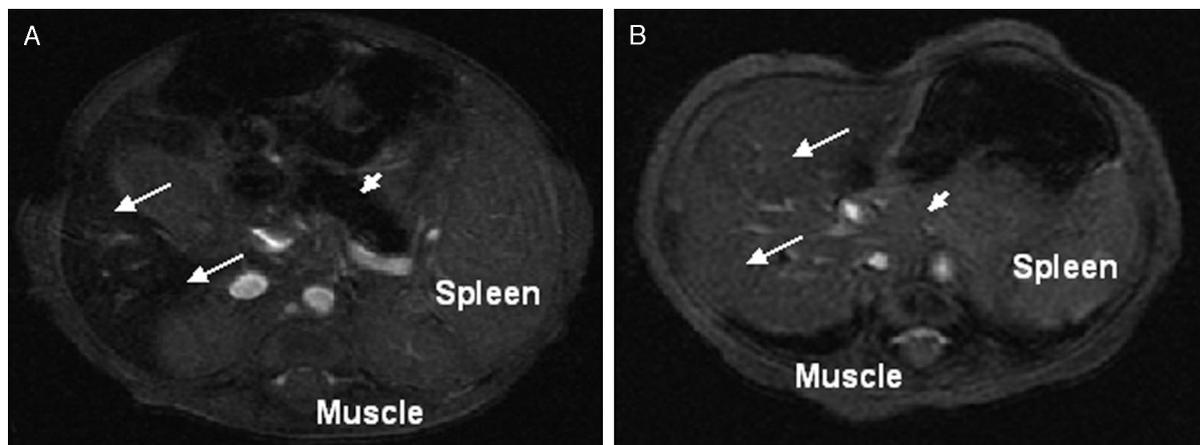
He was treated with therapy consisting of a combination of chelation and antioxidants<sup>16,17</sup> from day of life 1: acetylcysteine, 200 mg/kg per day, divided 3 times daily, orally for 21 doses;  $\alpha$ -tocopherol polyethylene glycol succinate, 25 IU/kg per day divided twice daily orally; deferoxamine, 30 mg/kg per day intravenously infused over 8 hours for 1 week or until the serum ferritin reached <500  $\mu$ g/L; selenium, 3  $\mu$ g/kg per day intravenously by continuous infusion for the length of hospitalization; and prostaglandin E1, 0.4  $\mu$ g/kg per hour intravenously increasing to 0.6  $\mu$ g/kg per hour over 3 to 4 hours with the infusion then maintained for 10 days. Supportive therapy consisted of fresh frozen plasma infusions, cryoprecipitate when clinically indicated, and parenteral nutrition. A buccal mucosal biopsy performed 17 days after commencement of chelation/antioxidant therapy (after transfer to Children's Memorial Hospital) failed to show stainable iron in the submucosal salivary glands.<sup>18</sup> His treatment was complicated by at least 2 episodes of bacterial sepsis ascribed to the deferoxamine therapy.<sup>1</sup> He ultimately recovered enough to be discharged from the hospital at 3 months of age, at which time his  $\alpha$ -fetoprotein (AFP) was 120 630 ng/mL and international normalized ratio (INR) was 1.79. At his 1-year follow-up, he had normal growth and development and his liver function had returned to normal (as shown in Table 1), although he had some residual hepatosplenomegaly.

Twin B was a healthy girl who discharged from the hospital within 48 hours of life. Because of our evaluation of her brother, and working on the premise that NH is an alloimmune gestational disease,<sup>9</sup> we were compelled to evaluate this child for evidence of liver disease. At 3 weeks of age she had remained well and on physical examination was found to have no jaundice, edema, ascites, or hepatosplenomegaly and had normal growth parameters. Her test results are shown in Table 1. MRI showed no evidence of iron overload in the liver or other tissues (Fig 1B). She was treated with vitamin E for 6 months, because her test results indicated some liver injury, specifically iron oxidative injury. With vitamin E being of low risk, we feel it should be applied in all such cases. She remained well at the 1-year follow-up and had normal laboratory results (as seen in Table 1).

### Twin Set 2

Dizygotic female twins were born by cesarean section at 37 weeks' gestation. The mother was gravida 3, para 2, and had 1 live unaffected child. The product of the second pregnancy was affected with NH and died at 2 months of age. The diagnosis was confirmed at autopsy. For the third pregnancy, the mother participated in a clinical trial of high-dose immunoglobulin during pregnancy to prevent severe recurrent NH.<sup>10</sup> The infants both had birth weights appropriate for gestational age, and the amniotic fluid volume was estimated to be normal. Both infants were carefully examined and tested at birth as part of this protocol.

Twin A appeared totally healthy and had a normal physical examination. Her test results indicated some liver injury (Table 1). She was also hypoglycemic, with blood glucose falling as low as 20 mg/dL. An MRI was not performed in this case, because it was



**Fig 1.** Axial T1, T2, and gradient-echo MRI was performed through the abdomen and lower chest of each of twin set 1 with attention to the liver, pancreas, and cardiac muscle. A, In twin 1A, the T2 signal intensity of the hepatic parenchyma (long arrows) and pancreas (short arrow) is markedly decreased relative to skeletal muscle and spleen, which are convenient internal references. There were also dark signals in the adrenal glands and myocardium that are not shown here. B, The T2 MRI from twin 1B showed normal signal intensity and appearance of the liver (long arrows) and pancreas (short arrow).

not part of the clinical research. She was treated with a cocktail of antioxidants and iron chelation<sup>16,17</sup> from day of life 1 (with chelation being continued for 21 days) and received intermittent fresh frozen plasma up to day of life 8 and intravenous glucose infusion. She remained clinically well and was discharged from the hospital on day 22 on full feeds with her INR at discharge being 1.2. She was treated with a full 6 months of vitamin E and was completely healthy with normal laboratory results at the 10-month follow-up (Table 1).

Twin B was also apparently healthy but demonstrated evidence of significant liver dysfunction (Table 1). She likewise had significant hypoglycemia with serum glucose values as low as 20 mg/dL. An MRI was performed for clinical reasons but was not technically adequate to interpret for extrahepatic siderosis. She received treatment with antioxidants and chelation<sup>16,17</sup> from day of life 1, with chelation being continued for 28 days. She had a protracted clinical course, requiring fresh frozen plasma support for coagulopathy for 17 days. Her peak serum bilirubin was: total, 13.9 mg/dL; direct, 4.7 mg/dL. Hypoglycemia necessitated prolonged continuous intravenous glucose infusion. She remained in the neonatal intensive care unit until discharge home on full feeds at 29 days of age with a discharge INR of 1.6. She was treated with a full 6 months of vitamin E and was completely healthy with normal test results at the 10-month follow-up (Table 1).

## DISCUSSION

The presentations and manifestations of NH in these sets of twins illustrate some important considerations related to the diagnosis of the disease. In each set, 1 twin exhibited liver failure. NH would not have gone undetected in any nursery setting in which clinicians were alert to its possibility as a cause for liver failure in newborns. The NH in the other twin in each set probably would have eluded detection if not for being twinned with a severely affected infant and/or being part of a pedigree of NH. This experience also brings to question the proper approach needed to determine if members of a pedigree are affected. Finally, it provides some insight into the etiology and pathogenesis of NH.

The unusual pattern of recurrence provided the clinical evidence that led to our hypothesis that NH is an alloimmune gestational disease. We recently completed a trial of gestational treatment to prevent recurrence of severe NH in women whose immediately previous gestation was affected.<sup>10</sup> In this trial, 15 women were treated through 16 pregnancies, all of which resulted in the birth of apparently healthy infants. All infants survived with medical or no treatment and are currently healthy. However, 12 infants had evidence of liver involvement with NH, indicating an actual recurrence rate of at least 75%. Only 4 infants had clinically evident liver disease, which would suggest an apparent recurrence rate of 25%. The other 8 affected infants only had elevated serum AFP and ferritin levels or elevated serum AFP alone. Treatment seemed not to reduce the recurrence rate but rather to modify recurrent NH so that it was not lethal to the fetus or newborn. The findings of this trial suggest that the combination of serum AFP and ferritin levels is sensitive for the detection of NH even in infants without major liver injury. Moreover, the results provide an explanation for the spectrum of illness observed in NH, namely an incomplete or modified alloimmune response.

Being confronted with the severely affected twin A (set 1) and having information that his sister, twin B, was entirely healthy led us to wonder about the

validity of our alloimmune hypothesis. We reasoned that alloimmunity against a common human fetal antigen, which we believe is the mechanism involved,<sup>19</sup> should affect both twins regardless of whether they were nonidentical. If twin B was not affected, the mechanistic hypothesis would be in doubt. Going back to our experience with the gestational-treatment trial, we saw that the majority of affected infants would not have been detected without sensitive testing. Although it is true that the spectrum of illness in the infants born after gestational treatment was shifted to the mild, it is evident that NH can produce liver disease without outward clinical disease. It has been observed that some infants diagnosed with NH are affected less severely, which may account for the ~20% who survive with medical therapy and the very few who have no liver failure.<sup>7,17,20</sup> It follows that there may even be some who have no clinical evidence of disease. On testing, we found twin B to have clear-cut evidence of liver disease, with high AFP and ferritin levels, therefore supporting our hypothesis. The findings from observing the second set of twins born after gestational treatment, 1 having liver failure and the other having clinically less significant disease, further confirms that alloimmune-mediated NH can produce a variable phenotypic expression in infants.

Differences among individuals in presentation and course of both autoimmune and alloimmune disease are poorly understood and require study. Severity of hemolytic disease (degree of anemia) may differ between twins born to rhesus-sensitized mothers.<sup>21</sup> This variation was ascribed to differences in fetal rhesus constitution (antigen polymorphism), gender, erythropoiesis, and hepatocellular function. Other possibilities among nonidentical siblings include variable antigen presentation caused by HLA differences. Similar considerations may apply in NH.

Our findings suggest that more sensitive approaches are needed for the detection of disease in analysis of recurrence in NH pedigrees. Although the expected recurrence rate in the subsequent pregnancy of a woman who has had 1 affected with NH is ~80%, the nonrecurrence rate is ~20%. That 20% could be "not affected" or "affected but it was not apparent." Of 12 apparently unaffected infants born after gestational therapy, 8 were actually affected when tested for the combination of serum AFP and ferritin.<sup>10</sup> Although these tests are clearly not specific for NH, they seemed to be sensitive for its detection in this study. Four infants had normal values for both AFP and ferritin. We have assumed them to be unaffected. However, it cannot be said with certainty that they were not affected to such a minimal degree that NH was not detected using these tests and would have been if a more sensitive test were applied. Identifying the "affected but not apparent" group may explain skipped pregnancies, absence of disease in twins and triplets, and perhaps even the 20% rate of nonrecurrence.

We recommend measuring serum AFP and ferritin as the currently most sensitive tests for detecting NH. In the context of severe liver disease in a newborn or the newborn child of a mother with a previ-

ously affected fetus or newborn, finding 1 or both to be elevated should lead to more definitive diagnostic testing such as MRI or oral mucosal biopsy. The accepted level of abnormality of ferritin warranting consideration of NH is 800 ng/mL.<sup>1,22,23</sup> The normal pattern of changing expression of AFP in the near-term infant requires careful consideration of gestational age when interpreting test results.<sup>24,25</sup> Normal values for term neonates are  $\leq 20\,000$  ng/mL, whereas to be considered as clearly abnormal, values must exceed 84 000 ng/mL in term infants and 200 000 ng/mL in 32-weeks-gestation premature infants.<sup>26</sup> It should be noted that there is a gap between normal and abnormal that is difficult to interpret. We caution that these tests are not specific for NH and thus have little positive predictive value for this specific diagnosis, and there are no data from which to estimate the rate of false-negative findings (ie, both values not abnormal in an infant with NH). One cause for a false-negative test for AFP is demonstrated in twin 1A. His initial AFP value was only 34 000 ng/mL, compared with a value at discharge 3 months later of 120 000 ng/mL. In this case, the relatively low AFP level at the time of diagnosis was probably related to hepatic synthetic failure, because AFP is made exclusively by the liver, and in this case it was associated with a serum albumin level of 1 g/dL and an INR of 4.7. In summary, obtaining the serum AFP and ferritin levels is currently the most sensitive test for addressing the question of whether the patient could have NH-related liver disease, whereas if the patient has clinical liver disease, it has no value in differential diagnosis (ie, little specificity or predictive value).

Twin 1A had iron overload of many tissues as determined by MRI (Fig 1A). His sister underwent MRI examination, which failed to show increased iron in any tissues (Fig 1B) despite her having evidence of NH-related liver disease. This 1 case does not inform on the mechanism of siderosis in NH, but it does add to the literature that suggests that the liver disease precedes and possibly is the cause of extrahepatic siderosis.<sup>27,28</sup> We did not routinely examine for siderosis in infants born after gestational treatment.<sup>10</sup> However, 4 infants who underwent percutaneous liver biopsy all showed iron in excess of normal. Only those with relatively severe liver disease received chelation therapy, and all were well at follow-up.<sup>10</sup> Again, this suggests that liver disease leads to siderosis in NH, not that iron overload leads to liver injury.

We recommend that treatment be determined by the degree of liver injury and impaired function. There is sparingly little evidence that the cocktail of chelation and antioxidants used in these patients actually influences outcome in NH. Survival of live-born infants with liver failure is  $<20\%$  with medical therapy alone.<sup>17,20,29</sup> In addition, the use of the cocktail is not without risk, particularly the risk of sepsis with deferoxamine.<sup>1</sup> Fully 50% of newborns we have treated with this cocktail have developed bacterial sepsis. Thus, we suggest that its use be reserved for infants with significantly impaired liver function (ie, INR  $> 1.8$ , persistent hypoglycemia) and that infants

with evidence of NH but no hepatic dysfunction receive vitamin E alone.

## CONCLUSIONS

Two sets of twins are reported with NH, with 1 twin presenting with liver failure and the second presenting with lesser clinical disease but with a biochemical picture strongly suggestive of NH. With the recurrence rate after the index case in a sibship as high as 80%, we recommend in light of these findings that apparently normal and asymptomatic newborn siblings following a case of NH should be evaluated carefully for evidence of NH by using serum levels of ferritin and AFP.

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*Pediatrics* 2005;116;e880

DOI: 10.1542/peds.2005-0784 originally published online November 15, 2005;

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