Neonatal Aortic Dilatation Secondary to Vitamin A Deficiency

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abstract

We report on a term neonate with unexplained respiratory distress, dilatation of the descending aorta, and low serum retinol concentration. The respiratory distress did not respond to conventional medical management and persisted for 22 days requiring an inspired oxygen fraction of 0.4 to 0.5 to maintain adequate arterial oxygen saturation. One week after intramuscular vitamin A therapy, the respiratory distress and requirement for supplementary oxygen resolved. Dilatation of the distal aorta resolved at 7 weeks of age. An association between vitamin A deficiency and aortic dilatation has previously been described in rats, but the association in humans has rarely been reported. We suggest that unexplained neonatal respiratory distress and a dilated aorta should prompt suspicion of vitamin A deficiency. An underlying infective or inflammatory process may give rise to a falsely low serum retinol concentration. Serum retinol and retinol binding protein concentrations in both the mother and infant should be used to guide vitamin A status, treatment, and subsequent response.

Dilatation of the aorta in the neonatal period is rare.[1] Even rarer is the association between vitamin A deficiency and dilatation of the descending aorta with respiratory distress. We report on the case of an infant boy who presented with unexplained respiratory distress in the presence of a dilated descending aorta and low serum retinol concentration. Vitamin A therapy resulted in the resolution of respiratory distress, as well as normalization of vitamin A biochemical status and the dilated aorta.

CASE REPORT

A full-term infant boy was born by elective cesarean delivery to nonconsanguineous parents, who conceived by in vitro fertilization technique after 6 years of infertility. The mother's height was 160 cm (BMI of 32). The mother, before conception and during pregnancy, was not following a restrictive diet. Antenatal fetal growth was normal. There were no risk factors for infection. The infant's weight was 2.6 kg (3rd to 15th percentile), length was 49 cm (15th to 50th percentile), and head circumference was 35 cm (50th percentile) plotted on World Health Organization child growth standards. His Apgar score was 9 at 1 minute and 10 at 5 minutes. Shortly after birth he developed subcostal recession, grunting, wet cough, and desaturations requiring up to 50% oxygen.

A chest radiograph revealed nonspecific patchy heterogeneous opacities bilaterally. There was no radiologic evidence of respiratory distress syndrome or cardiomegaly. With a working diagnosis of congenital pneumonia, he received intravenous ampicillin-cloxacillin and amikacin. Initial C-reactive protein (CRP) concentration and white blood cell count showed no evidence of infection and remained within normal limits

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Dr Mallett and Miss Simmonds performed the literature search, identified the association between vitamin A deficiency and aortic dilatation, and wrote the original draft of the manuscript; Ms Simmonds reviewed and edited the manuscript; Dr Kuppurajan reviewed and revised the manuscript; identified some of the references; authorized the final manuscript; wrote the abstract, title page, and contributors' list; and obtained consent from the parents; she was the attending pediatrician during the infant's NICU stay; Dr Narayanan is the pediatric cardiologist who provided the cardiology input to this manuscript and assisted in selecting the correct references, reviewing the images of the aorta, and ruling out other possible diagnoses associated with dilated aorta and provided the computed tomography images with this manuscript; Dr Balasubramanian performed the echocardiogram, identified the aortic dilatation on the basis of echocardiogram findings, examined the patient in outpatient clinics, and performed echocardiograms to monitor aorta size; he liaised with the pediatric cardiologist in obtaining the images and cardiac measurements that appear in this manuscript, reviewed and edited the manuscript, and critically appraised the content; Dr Ramakrishnan revised the manuscript; identified the references with Ms Simmonds and Dr Mallett; prioritized, selected, and organized the relevant references; liaised with other authors; maintained effective communication throughout and oversaw the entire process; and assisted the team in the writing of the manuscript; and all authors approved the final manuscript.

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until day 8. The blood culture taken at birth was sterile.

The infant received intravenous dextrose and electrolytes during the first week of life. Mother's expressed breast milk was commenced on day 4, and he reached full enteral feeds by the seventh day of life. He did not receive amino acids, intralipid infusion, or any form of multivitamin supplementation during this period. He tolerated his mother's expressed breast milk via an orogastric tube until the resolution of respiratory distress, after which he breastfed on demand.

Because the patient remained oxygen dependent on day 3, an echocardiogram was performed (Fig 1), which revealed a dilated aorta just beyond the level of the isthmus that measured 9 mm (z score + 2.96) and aorta at the diaphragm measured 9 mm (z score + 3.58). The rest of the aorta measured 6 mm at the valve (z score − 0.70), 8 mm at the sinuses (z score − 1.18), 7 mm at the sinotubular junction (z score − 0.15), 7 mm at the transverse arch (z score − 0.24), and 6 mm at the isthmus (z score + 0.93). The z scores were obtained with reference to the "Cardio Z" application,[2] which uses data from the regression equations published by Pettersen et al.[3] There was no pulmonary hypertension.

The patient continued to require 50% oxygen through nasal prongs. Arterial blood gas analysis was normal. Copious nasal secretions were noted on day 6, and respiratory secretions grew *Enterococcus* species. Piptazobactam and amikacin were prescribed in light of these findings. He received intravenous cefotaxime and co-amoxiclav because CRP remained elevated on day 9 in the absence of a clinical response to broad-spectrum antibiotic therapy. Blood cultures remained sterile. During the third course of broad-spectrum antibiotics, inflammatory markers eventually decreased to within normal limits on day 18, but his oxygen requirement, respiratory distress, and wet cough persisted until day 22.

In view of the patient's persisting oxygen requirement toward the end of the first week of life and an abnormal aorta, he was transferred to a regional pediatric cardiology center where a computed tomography (CT) angiogram confirmed a dilated descending aorta (Fig 2). Karyotype analysis was normal. Clinical features and CT findings were not suggestive of common genetic syndromes. Recent mutation analysis did not reveal any abnormality in the *FBN1* gene, thus ruling out Marfan syndrome. The infant also underwent a detailed assessment by a clinical geneticist who confirmed the absence of features suggestive of Marfan syndrome.

Noting a previous report linking vitamin A deficiency to neonatal aortic dilatation,[1] we measured serum vitamin A (retinol) concentration on day 8. Information on the mother's and infant's serum retinol concentration in relation to the infant's postnatal age in days and vitamin A therapy is provided in Table 1. The serum retinol concentration was low, measuring <0.34 μmol/L (deficiency = <0.7 μmol/L[4]). A separate serum sample collected on day 10 at the regional cardiac center and measured in a second laboratory also revealed a low serum retinol concentration (0.41 μmol/L). Both laboratories used the high-performance liquid chromatography method for sample analysis. The mother's serum retinol concentration of 2.19 μmol/L did not suggest deficiency (deficiency = <1.05 μmol/L[4]).

The patient received 4000 IU of vitamin A intramuscularly 3 times weekly for 3 weeks after informed verbal parental consent. After 3 doses, he was breathing room air by day 22. His respiratory distress and the wet cough resolved. His serum retinol concentration increased to 0.83 μmol/L (Table 1) after 6 doses of intramuscular vitamin A therapy. He subsequently received a routine oral multivitamin supplement containing 500 IU/day of vitamin A and received breast and formula feedings. His oxygen saturation, respiratory status, and serum retinol concentration remained normal at 1.2

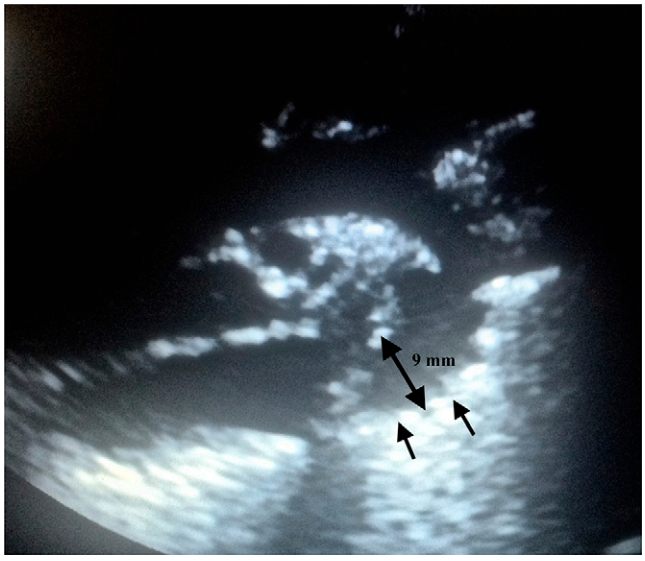

FIGURE 1
Echocardiogram of the aorta showing a dilated aorta beyond the isthmus (arrows) before vitamin A therapy.

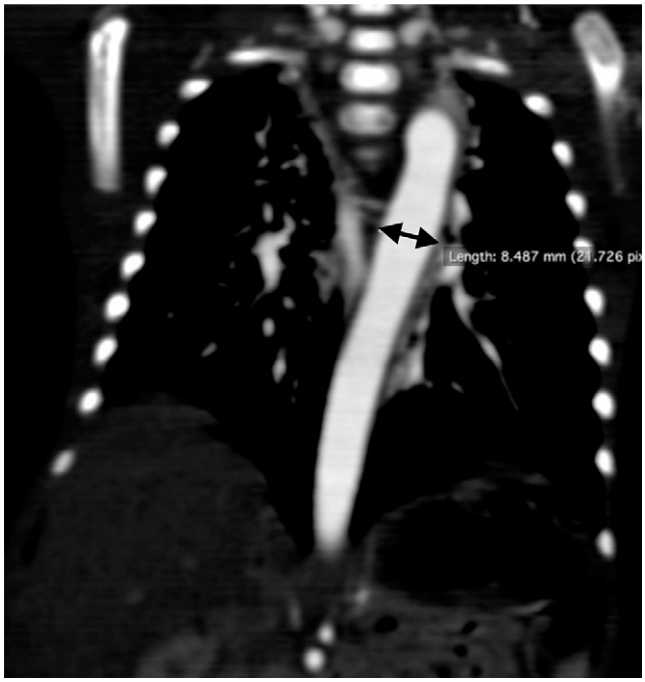

FIGURE 2
Contrast CT angiogram of the thorax reveals a dilated thoracic aorta (arrow) before vitamin A therapy.

μmol/L 3 months after stopping intramuscular vitamin A.

The infant's repeat echocardiogram at 7 weeks of age (Fig 3) revealed resolution of aortic dilatation. The aorta just beyond the isthmus measured 4.8 mm (z score^{2,3} = −1.52) and the aorta at the diaphragm measured 5.7 mm (z score^{2,3} = −0.44).

DISCUSSION

Cabano et al[1] reported neonatal aortic dilatation associated with vitamin A deficiency where a preterm neonate presented with bilateral microphthalmia, severe respiratory distress syndrome, and necrotizing enterocolitis. This neonate, unlike ours, also had a significantly dilated aortic root and a sinotubular junction and an ascending aorta.

Gatica et al[5] observed that rats fed vitamin A–deficient diets for 3 months showed oxidative stress and inflammation in the aorta. In another such experiment,[6] they demonstrated that a vitamin A–deficient diet altered the lipid metabolism of the aorta. The morphology of the aorta by light microscopy revealed an irregular intimal layer.[7] Transmission electron microscopy revealed large vacuoles and multivesicular bodies along the endothelium and subendothelial spaces caused by oxidative stress and inflammation due to vitamin A deficiency.

During early fetal development, vitamin A transfer from mother to the fetus is closely regulated.[8] Both vitamin A deficiency and excess may result in teratogenicity.[8] During advanced gestation, adequate maternal vitamin A intake is crucial to maintain newborn reserves and breast-milk retinol concentrations.[8] The mother of the infant we describe had a normal postpartum retinol concentration, but her status during pregnancy was unknown. Experiments in rats have suggested that maternal vitamin A deficiency during the first half of pregnancy resulted in abortions and congenital anomalies. A normal single postpartum maternal retinol concentration may not reliably reflect maternal vitamin A status during pregnancy. Analysis of primary antenatal blood samples, mother's milk, and cord blood might have provided further information regarding maternal vitamin A status but samples were unavailable.

Hulshof et al[9] found significant inter- and intralaboratory variations in measured retinol concentrations, predominantly attributed to poor analytical technique. We measured the infant's serum retinol concentration at 2 different standardized laboratories before

TABLE 1 Mother's and Infant's Serum Retinol Concentrations in Relation to the Infant's Treatment and Postnatal Age

Day of Life	Infant's Vitamin A Treatment Status	Infant's Serum Retinol Concentration, μmol/L	Mother's Serum Retinol Concentration in Relation to Her Infant's Day of Life, μmol/L
Day 8	Pretreatment	<0.34	2.19
Day 10	Pretreatment	0.41	—
Day 17	Intramuscular vitamin A therapy commenced	—	—
Day 22	Cessation of supplemental oxygen requirement after 3 doses of vitamin A therapy	—	—
Day 35	Posttreatment (6 doses of vitamin A therapy)	0.83	—
Day 117	Routine oral multivitamin supplement (500 IU/day of vitamin A) after cessation of intramuscular vitamin A therapy	1.2	—

Note that retinol concentrations <0.7 and <1.05 μmol/L are considered deficient in a neonate and adult, respectively. Empty cells denote that serum retinol concentrations were not measured.

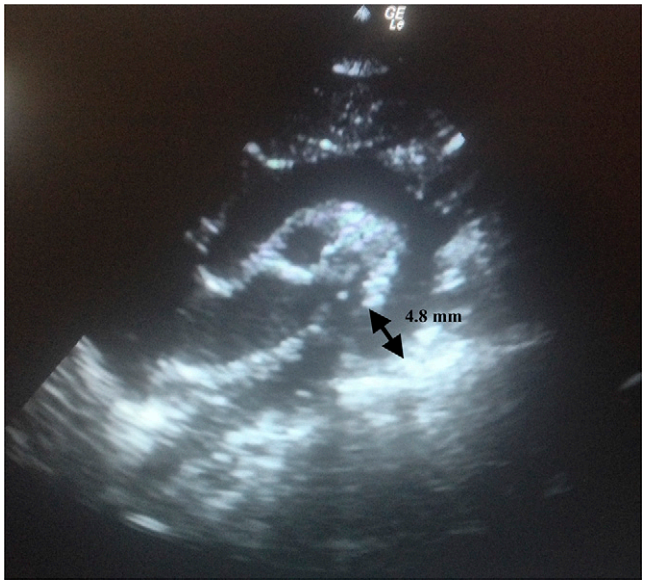

FIGURE 3
Echocardiogram of the aortic arch reveals a normal-sized aorta (just beyond the isthmus - denoted by arrow) for age (after vitamin A therapy).

initiating treatment. Both reported a low serum retinol concentration.

Retinol circulates in equimolar amounts with retinol binding protein, which is a negative acute-phase reactant.[10] Stephensen and Gildengorin[11] found low mean serum retinol concentrations in subjects with a CRP concentration of >10 mg/L. In our case, there were no maternal risk factors for early-onset sepsis. The infant's inflammatory markers increased for the first time on day 9; however, the finding of a dilated aorta on echocardiography was noted on day 3 when the inflammatory markers were normal. The respiratory secretions later grew *Enterococcus* species and the CRP concentration increased to 64 mg/L on day 9 but normalized by day 18; however, the infant was still oxygen dependent until day 22, ruling out infection as a single cause for his symptoms. Although it is possible that a postnatal infective or inflammatory process might have given rise to a low concentration of serum retinol, it would neither explain the presence of echocardiographic findings noted as early as the third day of life nor the clinical response to retinol administration.

Gatica et al[6] found that the changes observed in the aortas of vitamin A–deficient rats normalized after vitamin A supplementation. Similarly, Cabano et al[1] documented that the significant aortic dilatation resolved completely upon vitamin A supplementation. Our case showed a similar response to treatment; aortic diameter normalized and the respiratory distress coupled with oxygen requirement resolved only after initiating vitamin A therapy.

Although we have not been able to explain why the adequately nourished neonate of an apparently healthy mother should be born with low retinol status, we indicate that the improvements in biochemical and functional (clinical) state after retinol administration suggest that vitamin A deficiency was responsible for his condition at birth. Although the mother appeared healthy and her postdelivery retinol concentration did not suggest deficiency, her vitamin A status during conception and pregnancy remains unknown. She may have had an unidentified subclinical deficiency due to intestinal malabsorption of micronutrients.

A diagnosis of vitamin A deficiency should be considered in a neonate who presents with unexplained respiratory distress and a dilated aorta in the neonatal period. Serum retinol concentration should be interpreted with caution in the presence of acute infection or inflammation, which may be responsible for falsely low retinol concentrations. Serum retinol and retinol binding protein concentrations of mother and infant should be measured in an accredited laboratory before a trial of vitamin A therapy.

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