Resolution of neonatal posthemorrhagic ventricular dilation coincident with patent ductus arteriosus ligation: case report

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Preterm infants commonly present with a hemodynamically significant patent ductus arteriosus (hsPDA). The authors describe the case of a preterm infant with posthemorrhagic ventricular dilation, which resolved in a temporally coincident fashion to repair of hsPDA. The presence of a PDA with left-to-right shunting was confirmed at birth on echocardiogram and was unresponsive to repeated medical intervention. Initial cranial ultrasound revealed periventricular-intraventricular hemorrhage. Follow-up serial ultrasound showed resolving intraventricular hemorrhage and progressive bilateral hydrocephalus. At 5 weeks, the ductus was ligated with the goal of improving hemodynamic stability prior to CSF diversion. However, neurosurgical intervention was not required due to improvement of ventriculomegaly occurring immediately after PDA ligation. No further ventricular dilation was observed at the 6-month follow-up.

Systemic venous flow disruption and abnormal patterns of cerebral blood circulation have been previously associated with hsPDA. Systemic hemodynamic change has been reported to follow hsPDA ligation, although association with ventricular normalization has not. This case suggests that the unstable hemodynamic environment due to left-to-right shunting may also impede CSF outflow and contribute to ventriculomegaly. The authors review the literature surrounding pressure transmission between a PDA and the cerebral vessels and present a mechanism by which PDA may contribute to posthemorrhagic ventricular dilation.

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KEYWORDS hydrocephalus; patent ductus arteriosus; intraventricular hemorrhage; premature infant; posthemorrhagic ventricular dilation; neonatal

THE ductus arteriosus facilitates blood flow from the pulmonary artery (PA) to the aorta during gestation. This vascular pathway typically closes within hours after birth, but can remain patent, especially in infants of decreased gestational age.^{1,2} An estimated 20% of premature neonates are born with a patent ductus arteriosus (PDA).^{3–5} A hemodynamically significant PDA (hsPDA) can be associated with harmful alterations in vascular flow, volume, and pressure that are experienced by the brain.⁶ Although there is not a consensus on defining a threshold for hsPDA, Shepherd and Noori recently suggested criteria for objective measures of PDA flow (e.g.,

ductal diameter, shunt pattern) and clinical factors (e.g., prematurity, periventricular-intraventricular hemorrhage [PIVH]) that are associated with hemodynamic significance.⁶ The abnormal vascular effects of left-to-right cardiac shunting can increase the risk of neonatal PIVH due to rupture of fragile germinal matrix microvasculature.⁷ Circulatory changes attributed to hsPDA that correlate with IVH severity include retrograde flow in cerebral arteries,⁸ decreased right ventricular output,⁹ decreased diastolic blood pressure,^{7,10} and decreased superior vena cava (SVC) flow rate.¹¹ Infants with hsPDA can have elevated central venous pressure (CVP)^{7,12} and may demonstrate an

ABBREVIATIONS CVP = central venous pressure; FOHR = frontal-occipital horn ratio; FTHR = frontal-temporal horn ratio; hsPDA = hemodynamically significant PDA; OFC = occipital frontal circumference; PA = pulmonary artery; PDA = patent ductus arteriosus; PHVD = posthemorrhagic ventricular dilation; PIVH = periventricular-intraventricular hemorrhage; SVC = superior vena cava; VLBW = very low birth weight; VSGS = ventriculosubgaleal shunt.

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inverse trend between PDA diameter and cerebral oxygen saturation.^{13,14} There is also evidence that hsPDA may have a negative impact on neurodevelopment.^{15–17}

Increases in PDA size correlate with increased rates of adverse sequelae (e.g., pulmonary hypertension, PIVH)^{9,18} and are important factors in predicting future ductus patency and the need for treatment.¹⁹ Treatment strategies for hsPDA include conservative monitoring for spontaneous closure, pharmaceutical intervention, endovascular coiling, and surgical ligation.^{20,21} Ligation is generally reserved for hsPDA unresponsive to conservative or medical management.²² In the US, there is considerable variation in PDA diagnosis and treatment by geographic region, with ligation rates in PDA-bearing infants ranging from 4% to 28%.⁵ In preterm infants overall, the incidence of PIVH is 25%–30%, with grade III or IV hemorrhage comprising approximately one-third of bleeding events.^{3,23} Nearly 75% of babies with grade III and IV PIVH demonstrate persistent posthemorrhagic ventricular dilation (PHVD), and 75% of these neonates with PHVD progress to a formal diagnosis of hydrocephalus requiring CSF diversion.²⁴

In this work, we report the spontaneous resolution of PIVH-associated ventriculomegaly immediately following hsPDA ligation. Within the body of literature on neonatal ventriculomegaly and PIVH-associated hydrocephalus, a rigorous examination regarding the time course of ventricular enlargement is lacking. Additional mechanistic insight is required regarding the origins of neonatal ventricular dilation and the resolution of this phenomenon when it occurs.²⁵ To our knowledge, the reversal of progressive PHVD has an unreported association with hsPDA ligation. Whereas the pathway for arterial pressure transmission to the systemic venous circulation and consequent venous flow disruption in the brain has been well established in hsPDA, the link with neonatal ventriculomegaly has not been explored. We believe this work will serve to facilitate further targeted investigation, and we propose a mechanism through which such an effect may occur.

Case Report

History and Examination

The patient was male, born weighing 615 g at 25 weeks' gestation to a 35-year-old mother (G2P1) via repeat cesarean section due to fetal breech position. The pregnancy was complicated by superimposed preeclampsia with severe features, and fetal cardiac decelerations. The boy was admitted to the neonatal intensive care unit for management of prematurity, extremely low birth weight, and bronchopulmonary dysplasia. He received multiple courses of dopamine and stress-dose hydrocortisone for blood pressure support.

High-frequency oscillatory ventilation was used for worsening respiratory acidosis and pulmonary edema secondary to suspected PDA. The presence of a PDA with significant left-to-right cardiovascular shunting was confirmed on echocardiogram. Pharmaceutical intervention was implemented with 2 rounds of acetaminophen, followed by 2 rounds of indomethacin. Serial echocardiograms demonstrated continued patency of the ductus despite medical intervention, and further revealed a small

FIG. 1. Preoperative PDA echocardiogram images and Doppler flow. **Upper:** Representative 2D imaging of the PDA with and without Doppler color. **Lower:** Doppler tracing of PDA blood flow showing pulsatile left-to-right shunt pattern. Ao = aorta. Figure is available in color online only.

patent foramen ovale with normal right ventricle size, a mildly dilated left ventricle, and physiological tricuspid valve insufficiency.

Initial cranial ultrasound showed enlarged lateral, third, and fourth ventricles with IVH and bilateral subependymal hemorrhage consistent with grade III PIVH. Follow-up ultrasounds revealed progressive bilateral ventricular enlargement with resolving IVH and no new bleeding. The patient had a progressively increasing frontal-occipital horn ratio (FOHR) above 0.55, progressively full-but-soft fontanelle, and splayed sutures. Multidisciplinary discussion with cardiac and neonatal intensive care teams encouraged improved hemodynamic stability prior to a cranial temporizing surgery (e.g., ventriculostomy shunt [VSGS]), with the consensus that PDA ligation might contribute to improved cardiopulmonary function.

Operation, Postoperative Imaging, and Follow-Up

At week 3 of life, the PDA measured 1.7 mm in diameter on echocardiograms, with a pulsatile, left-to-right shunting pattern (Fig. 1). Additional measurements suggestive of hemodynamic significance included a left atrium/aortic root ratio of 1.7, a left PA end diastolic velocity of 16 cm/sec, and a left ventricle output of 428 ml/kg/min.⁶ No reversal of flow was noted in the descending aorta. On day 35 of life, the patient underwent surgical ligation of the ductus arteriosus via a posterolateral fourth interspace thoracotomy. Postoperative echocardiograms revealed ductal hemostasis, a widely patent aortic arch, and normal cardiac ventricular function.

The plans for cranial temporizing surgery were influenced by coincident changes in postligation measurements of ventricular size. Figure 2 displays data from all cranial ultrasounds obtained between weeks 1 and 15 of life, including calculated measures of FOHR (Fig. 2A), frontal-temporal horn ratio (FTHR; Fig. 2B), temporal horn width

FIG. 2. Graphs showing time course data obtained using 4 techniques of ventricular size estimation. Cranial ultrasound images were used to calculate (A) FOHR, (B) FTHR, (C) temporal horn width, and (D) maximum bilateral frontal horn width over time. Ventricular measurements were made in triplicate, once each by 3 individuals, with error estimates between measurements displayed as $\pm$ SD. The day of hspDA ligation is indicated by the vertical red line. Figure is available in color online only.

(Fig. 2C), and anterior horn width (Fig. 2D), along with the timing of PDA ligation (red line). Representative cranial ultrasound coronal sections are supplied in Fig. 3. Serial ultrasound images showed a transition between worsening and improvement of ventriculomegaly occurring immediately at the time of PDA ligation. There was no substantial change in the distribution of intraventricular clot during this time frame. As a result, neurosurgical intervention was averted. Immediately prior to ligation, the occipital frontal circumference (OFC) began to increase past growth curves, above the 10th percentile, to reflect the ventricular size change (Fig. 4). This upswing normalizes thereafter to a trajectory matching the 5th percentile. This may have been due to difference in OFC measuring techniques between individuals.

At 3 months of age, echocardiogram revealed normal cardiac biventricular size and function, unchanged mild patent foramen ovale, a patent aortic arch, and stasis of

flow through the prior PDA site. Cranial ventricular size and head circumference remained stable, and no signs of transient bradycardia or apnea were present (Fig. 4). The fontanelle was soft and sunken. No temporizing measures for CSF extraction were performed throughout the patient's clinical course. No further ventricular dilation was observed at 6 months of follow-up, and no shunt has been required.

Discussion

In this work we present a case of ventriculomegaly resolution that occurred in the absence of intracranial intervention, immediately following hspDA closure. According to recently suggested guidelines to define the hemodynamic significance of PDA flow, this case meets 4 of the 6 objective criteria (size > 1.5 mm at gestational age < 26 weeks, pulsatile shunt pattern, left atrium/aortic

FIG. 3. Representative cranial ultrasound images. Images are displayed from days of life 3, 10, 34, 38, 48, and 106 and correspond to arrows on the timeline below. The day of hsPDA ligation is indicated by the red arrow. Figure is available in color online only.

root ratio > 1.4 , and left ventricle output > 300 ml/kg/min) with 2 additional contributing clinical factors (prematurity, IVH).⁶ Figure 5 provides a schematic representation for possible vascular feedback between the cardiac and intracranial compartments, using known systemic hemodynamic consequences of hsPDA to support a plausible connection with ventriculomegaly. Left-to-right shunting of blood through a PDA allows mixing of the high-pressure systemic circulation and low-pressure pulmonary circulation.²⁶ Infants with hsPDA have decreased right ventricle output, increased SVC resistance, and decreased cerebral oxygen saturation.^{9,11,13} Prior reports suggest that PDA-associated preloading of the right heart contributes to venous congestion within the dural venous sinuses.¹³ Very low birth weight (VLBW) infants often have near- or sub-atmospheric intracranial pressure, making small changes in systemic circulation likely to influence cerebral venous hemodynamics.^{27,28} Elevated CVP and impaired venous outflow from the sinus represent compelling potential sources of theoretical impairment for CSF egress (Fig. 5).

The data supplied here convey a correlation of PDA clo-

FIG. 4. OFC and weight change over time. OFC (cm) and weight (kg) were plotted along a Fenton growth chart for premature infants with gestational age (weeks) as the x-axis. From top to bottom, dashed lines indicate the 97th, 90th, 50th, 10th, and 3rd percentiles. Figure is available in color online only.

sure with ventricular size/OFC normalization (Figs. 2–4) and represent the first documentation of this temporal relationship in the literature. The results must be interpreted with caution and should not be viewed as proof of a link between hsPDA, cerebral hemodynamics, and ventricular outflow. Although hydrocephalus is a well-documented consequence of PIVH,^{3,23} our case suggests that the unstable hemodynamic environment due to left-to-right shunting may also impede CSF outflow and, in addition to an underlying degree of IVH, may contribute mechanistically to ventriculomegaly. This relationship may not have been previously identified due to the nationwide variation in PDA diagnosis and treatment strategy,⁵ or to the lack of a definition surrounding PDA hemodynamic significance.⁶

It has been previously shown that a systemic hemodynamic change can immediately follow hsPDA ligation. Bissonnette and Benson detected both acute decline in

FIG. 5. Proposed mechanism to explain hydrocephalus in the context of hsPDA. Left-to-right shunting via hsPDA diverts blood from the systemic arterial circulation to the PA. Preloading of the right heart can result in increased CVP and SVC resistance, leading to venous congestion in the brain and reduced CSF outflow. Dashed lines indicate increased fluid resistance. Figure is available in color online only.

CVP and increase in diastolic cerebral artery velocity during surgical PDA ligation,⁷ a finding supported by others.^{10,29} In an investigation of the natural history of VLBW infants with posthemorrhagic ventriculomegaly, 38% had arrest of cerebral ventricular enlargement and did not require treatment.²³ Thus a percentage of PVHD cases spontaneously resolve. In a multiinstitutional study of premature newborns with IVH grade III or IV, 19% of infants (28/145) did not require any temporization.²⁴ Unfortunately, a majority of literature reports have not supplied time course details of ventricle size change, which would help to support or deny this relationship. One illustrative case report by Allan et al. suggests that resolution of ventricular dilation without intervention can occur over a 2- to 4-week time frame, a longer time frame than seen here.³⁰ The use of temporizing measures (i.e., lumbar puncture, fontanelle tap, external ventricular drainage, ventricular reservoir, VSGS) for severe PHVD further confounds interpretation of trends in the literature.^{31–33} Resolution of ventriculomegaly after temporizing interventions may be attributed to the intervention itself—by reducing CSF protein content, red blood cells, or inflammatory factors—or

to the time delay and systemic hemodynamic changes afforded by the intervention. Kaiser and Whitelaw provide a case similar to ours, in which a VLBW infant of 28 weeks' gestation with PHVD experienced a rapid decline in ventricular width over the course of a day.³² This decline followed 4 serial lumbar punctures performed 1 week prior. It is interesting to note that this patient's course was complicated by a PDA, although a link to PDA extent, treatment, monitoring, or resolution was not explored. Further research is required to examine the physiological nature and timing of spontaneous ventriculomegaly resolution.

The mechanism by which ventriculomegaly may appear and resolve following IVH has been underexplored to date.²⁵ A number of theories exist for posthemorrhagic CSF outflow disruption, including 1) temporary thrombotic or proteinaceous obstruction of CSF outflow through foramina or arachnoid granulations; 2) inflammatory-mediated chemical arachnoiditis; 3) posthemorrhagic distortion of normal CSF and/or vascular pressure gradients; and 4) impaired lymphatic CSF resorption.^{25,34–36} Whereas prior models accepted the arachnoid granulation as a primary site of CSF outflow, current understanding places

additional importance on interstitial CSF flow.^{36,37} In premature infants, the arachnoid villi and granulations are in development, suggesting other routes of CSF drainage.^{38,39} In animal models, venous drainage of CSF via granulations serves as an auxiliary system, with increases in flow at times of elevated intracranial pressure.⁴⁰

The patient described in this report would probably have undergone placement of a VSGS prior to PDA ligation had he been hemodynamically stable. The preceding PDA ligation allowed visualization of ventricular size reduction in the absence of cranial temporizing intervention. The proportion of infants who demonstrate resolution of ventriculomegaly or a change in cerebral hemodynamics after PDA closure is unknown. This question may be addressed in the future by rigorous collection of hemodynamic data (e.g., cranial arterial/venous Doppler ultrasound, echocardiogram, systemic venous pressure) and modern neuroimaging data (e.g., structural MRI, CSF flow sequences, MR perfusion) during a period of transient ventriculomegaly. Few studies of hydrocephalus include data on hsPDA severity or closure time. This report of hsPDA ligation and PHVD highlights the potential connection between systemic hemodynamics and CSF flow in neonates, and provides new data from a single patient regarding the time course along which ventriculomegaly may improve. Furthermore, this work suggests a role for future prospective data collection regarding PDA, intracranial hemodynamics, and ventricular size.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chiarelli, Vanstrum. Acquisition of data: Chiarelli, Vanstrum, Wang, Rea. Analysis and interpretation of data: all authors. Drafting the article: Chiarelli, Vanstrum, Borzage, Chu, Rea. Critically revising the article: Chiarelli, Vanstrum, Borzage, Chu, McComb, Krieger. Reviewed submitted version of manuscript: Chiarelli, Vanstrum, Borzage, Chu, Wang, McComb, Krieger. Approved the final version of the manuscript on behalf of all authors: Chiarelli. Study supervision: Chiarelli.

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