CLINICAL VIGNETTE

Alagille Syndrome and Pregnancy: Anesthetic Considerations

Peter Drocton, MD and Steven Tham, MD

A 31-year-old G3 P0202 female was referred to the Preanesthesia Clinic for evaluation of expectant management of labor. Patient stated she was born with Alagille syndrome (biliary hypoplasia) and underwent biliary shunt placement in infancy. Her disease continued to manifest as chronic malabsorption of fat-soluble vitamins with chronic cholestyramine use. During her first pregnancy, she was admitted to the ICU at a quaternary-care hospital for severe coagulopathy and vitamin K deficiency. She was listed for liver transplantation but after rapid correction of her coagulopathy with vitamin K administration and fresh frozen plasma (FFP), she was delisted. The infant was delivered vaginally at 31 weeks without further complication. The hepatology service recommended additional follow up, as it was felt that the patient would likely require liver transplantation in the future. However, the patient opted not to follow up. She reported a second pregnancy and spontaneous delivery at 36 weeks at a different community hospital without complication. In both cases, the patient reports that she did not receive labor analgesia or anesthesia, which review of outside records confirmed.

The patient was been seen by the GI (gastroenterology)/ hepatology service at our hospital at 18 weeks gestation. Her lab values were notable for: low albumin 3.0 g/dL and high alkaline phosphatase 408U/L, AST 91U/L, ALT 135U/L, total bilirubin 1.3mg/dL. Platelet count was 125,000. She was continued on ursodiol; started empirically on 100mcg phytonadione (vitamin K) daily; and restarted on cholestyramine 4g twice daily.

Her evaluation in the Preanesthesia Clinic was performed at 31 weeks gestation. Her pregnancy had been progressing without incident, and she reported good compliance with her liver medications. She was otherwise healthy without any significant medical issues. Given her underlying disease, an echocardiogram was obtained which showed: an ejection fraction of 65-70%; normal systolic function; normal wall motion without irregularities; and no significant valvular disease. Laboratory studies since her initial hepatology evaluation were not significantly changed, with a platelet count at 149,000. Lumbar MRI showed: normal conus medullaris terminating at T12-L1; severe disc height loss and mild spinal canal stenosis at L1-L2; and otherwise normal neural foramina and spinal canal at all other lumbar areas. Of note, INR was 0.98.

The patient was admitted at 36 weeks for induction of labor for cholestasis. Her lab liver function tests were again noted to be elevated, and her INR had increased to 2.03. The Anesthesia service was again consulted and the patient counseled on options for labor analgesia; neuraxial analgesia was not offered at this time given the elevated INR value. The GI/hepatology and medicine services were consulted given her coagulopathy. Though she had been compliant with phytonadione, it was postulated that absorption was inadequate and IV vitamin K was given with improvement in INR to 1.18. The patient's labor progressed quickly and she opted to proceed without epidural analgesia. An infant at 1950g was delivered vaginally (APGAR 9 at one minute and 9 at five minutes); estimated blood loss was 350cc. The patient's postpartum course was otherwise uneventful and she was discharged on post-partum day 3. She was again recommended to avoid future pregnancies and to follow up with the hepatology service for evaluation for eventual liver transplantation.

Discussion

Alagille syndrome is an autosomal dominant genetic disorder due to a mutation in the JAG1 gene or NOTCH 2 gene. The syndrome is characterized by paucity of hepatic interlobular bile ducts. Clinical manifestations extend beyond the liver to include four additional "main systems" used in the "Classic Criteria" used to make the diagnosis. In addition to the liver, these include the heart, skeleton, face, and eye.[1]

The liver is the most affected organ in Alagille syndrome, and an early sign in an affected individual is neonatal jaundice due to conjugated hyperbilirubinemia. Chronic cholestasis results in pruritis, cirrhosis and coagulopathy. Vitamin K and other fat-soluble substances are deficient. Anomalies in other systems are seen in varying degrees, including cardiac defects such as peripheral pulmonic stenosis, tetralogy of Fallot, ductus arteriosus, or coarctation of the aorta. Skeletal defects can include "butterfly vertebra", due to failure of fusion of the anterior vertebral arches and fusion of adjacent vertebrae or spina bifida occulta. In the eye, anterior chamber defects can be observed although visual prognosis is usually good. Alagille syndrome often results in mild dysmorphic facial features including a prominent forehead, deep-set eyes with hypertelorism, up slanting palpebral fissures, depressed nasal bridge, straight nose with bulbous tip, large ears, prominent mandible, and pointed chin.[1,2]

Anomalies in other systems not used in the "Classic Criteria" can also be present, including vascular problems including

Moyamoya syndrome, cerebral vascular anomalies, and reno-vascular anomalies. Renal tubular acidosis can result from Alagille syndrome, as well as renal structural problems such as renal dysplasia, cysts, and ureteropelvic obstruction.[2]

Two specific clinical features of Alagille syndrome should be carefully evaluated in a parturient prior to anesthetic care. Coagulation status should be verified, as a severe coagulopathy can increase the risk of spinal hematoma from needle insertion during a neuraxial anesthetic technique, which includes spinal and epidural procedures. An expanding spinal hematoma can have devastating neurologic consequences if not promptly recognized and addressed. If present, butterfly vertebra can cause anatomic abnormalities such as severe scoliosis and can make neuraxial anesthetic technique difficult or even contra-indicated. A thorough evaluation of vertebral anatomy is prudent before neuraxial anesthesia.

Although our patient delivered vaginally without epidural analgesia, the patient's coagulation status was monitored carefully in the peripartum period in the event a surgical procedure became necessary. Early referral to Preanesthesia Clinic also allowed enough time to obtain a lumbar MRI to evaluate for vertebral anomalies. This case demonstrates the importance of early identification of patients with unusual or complicated disease and careful coordination of care to ensure optimal outcomes.

REFERENCES

1. **Turnpenny PD, Ellard S**. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet*. 2012 Mar;20(3):251-7. doi: 10.1038/ejhg. 2011.181. Epub 2011 Sep 21. PMID: 21934706; PMCID: PMC3283172.
2. **Hamosh A**. Alagille Syndrome 1; ALGS1. http://omim.org/entry/118450 (Accessed 4 Feb 2021).