A Neonate With Pallister-Hall Syndrome and Arrhythmia

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Abstract
We anesthetized a full-term male infant with a history of supraventricular tachyarrhythmias on three occasions: days-of-life 6, 30, and 131. The patient initially carried a diagnosis of VACTERL syndrome but because of intraoperative findings and subsequent genetic study, was diagnosed with Pallister-Hall syndrome. Cardiac arrhythmias have not previously been reported with this syndrome. We further review known aspects of Pallister-Hall syndrome that may complicate anesthetic management and may alert clinicians to subclinical cases.

Introduction
Pallister-Hall syndrome (OMIM # 146510) is a rare complex of congenital abnormalities: polydactyly, imperforate anus, hypopituitarism, hypothalamic hamartoblastoma, renal anomalies, and bifid or shortened epiglottis. Other reported abnormalities associated with Pallister-Hall syndrome (PHS) include colonic aganglionosis, epilepsy, renal abnormalities, hypopituitarism, and stenosis of the cricoid cartilage. PHS has not been previously associated with significant or life-threatening arrhythmia, although an association with congenital cardiac defects has been reported at least once. We report the anesthetic management of a neonate with the novel combination of PHS and supraventricular tachyarrhythmia (SVT).

Case Report
A male infant was born at term weighing 3.5 kg. He had been intubated for respiratory distress at birth with a 3.5 mm cuffed oral endotracheal tube. Shortly after birth, polydactyly (six fingers bilaterally) was also noted, along with an imperforate anus, which was surgically corrected on postnatal day 3 without complication. As VACTERL syndrome was suspected (a relatively common sequence of vertebral anomalies, anal atresia, cardiac defects, esophageal atresia, renal defects, and limb malformations), the patient was diagnosed with a single atrium by screening echocardiogram. On the fourth day of life, the patient developed two episodes of pallor and hypotension secondary to SVT, lasting over two minutes each. The arrhythmias did not require cardioversion and were responsive to amiodarone. The patient was thereafter maintained on an amiodarone infusion (7 μg/kg/hr).
The patient was scheduled for direct laryngoscopy and insertion of a Broviac catheter at 6 days of age. He was transported to the OR with a continuous amiodarone infusion and with defibrillator pads attached. Anesthesia was induced with two boluses of propofol (5 mg/kg each) and fentanyl, 3 μg/kg, and maintained with sevoflurane in 100% oxygen. The Broviac catheter was placed in the right subclavian vein without complication. The patient was extubated to permit diagnostic direct laryngoscopy and bronchoscopy by otolaryngologists. Anesthesia was then maintained with a propofol infusion at 100 μg/kg/min. Bronchoscopy revealed diffuse mild inflammation of the trachea and carina while laryngoscopy showed a shortened, malformed epiglottis (Figure 1). The patient was re-intubated with a 3.5 mm cuffed oral tube and transported back to the neonatal ICU without further SVT. At that time, the diagnosis of PHS was considered and a genetics consult was obtained.

We were requested to anesthetize this patient again at 30 days of age for tracheostomy and gastric tube placement. Both procedures proceeded without complication. The patient remained ventilated and dependent on partial parenteral nutrition, with appropriate weight gain. At the 131st day, he was diagnosed with ureteropelvic-junction obstruction, consistent with the known renal abnormalities associated with PHS. He was anesthetized for bilateral nephrostomy tube insertion under general anesthesia in the prone position, again without complication.

**Discussion**

PHS has some phenotypic overlap with features of the VACTERL sequence. VACTERL has sporadic inheritance, but PHS is an autosomal dominant, monogenetic disorder resulting from a frameshift deletion in the zinc-finger transcription factor Gli3. It has been suggested that PHS is indistinguishable from congenital hypothalamic hamartoblastoma syndrome, CAVE (cerebral-acro-visceral early lethality) multiplex syndrome, and should replace the diagnosis of polydactyly-imperforate anus-vertebral anomalies (PIV) syndrome in most cases. PHS shares some features of Grieg cephalopolysyndactyly syndrome (GCPS), although it has been determined to be clinically distinct. Interestingly, both PHS and GCPS are known to result from errors at the Gli3 gene. One point of distinction is that PHS is due to a dominant-negative loss-of-function frameshift or nonsense mutation in the gene product, whereas GCPS is usually due to haploinsufficiency of functional protein.

The genetic diagnosis of this patient was based on the pattern of the congenital anomalies and genetic testing. The anomalies included anal atresia, undescended testes, ureteropelvic junction obstruction, extra
lumbar vertebrae, postaxial polydactyly of the hands, single atrium, and shortened malformed epiglottis. PHS is the only described syndrome associated with all these abnormalities. Chromosome analysis including FISH for DiGeorge syndrome was reported as normal [46,XY, ish22q11.2 (HIRAx2)]. Affymetrix version 6.0 whole genome chromosome SNP/CN microarray (CSM) copy number analysis was normal. Based on these tests, segmental aneusomy is an unlikely cause of the baby’s abnormalities. Genetic testing of Gli3, the gene associated with Pallister-Hall syndrome, was not performed. According to the genetics consultation, a negative result in Gli3 testing would not change the diagnosis of PHS in this baby. Only the absence of hypothalamic hamartoma could cast doubt on this diagnosis in the future.

Anesthetic management of PHS patients has been previously reported once, and was successful because difficult laryngoscopy was anticipated. Interestingly, in the reported patient, the hypoxia and extreme difficulty with intubation experienced before he was 3 years of age were not seen later; laryngoscopy was easy at 5 1/2 years of age. This suggests that these patients may outgrow the problems in their airway management; but, obviously, only further procedures under general anesthesia will demonstrate this. Difficult airway management is not certain; in fact, our case raises another possibility to which anesthesiologists should be alert: If an adolescent or adult patient presents with low to normal intelligence, but with polydactyly and imperforate anus or a history of surgical correction, we should consider the possibility of asymptomatic PHS and even of associated SVT. Another case series from 2000 discussed elective laryngoscopy of 40 patients with either PHS or GCPS, ages 1 day to 74 years, and found a broad range of severity in those with PHS. These patients are often term infants of normal weight (as in this case) and, when surviving to childhood, can have normal intelligence with an asymptomatic malformed epiglottis, which was seen in 15 of 26 PHS patients in this series. The authors also noted another important distinction of PHS from GCPS beside the genetic one: none of the 14 probands with GCPS had a cleft epiglottis.

SVT has never been previously reported concomitantly with PHS. Although both are rare, the possibility that they were coincidental cannot be entirely excluded. SVT is the most common arrhythmia of neonates, occurring as frequently as one in 250-1,000 infants. Most cases are sporadic, although 7% have a first-degree relative with a known incident of SVT. There is also a familial variant of Wolf-Parkinson-White syndrome that can present with SVT. This suggests that SVT, on at least some occasions, may have a genetic basis. One group who reviewed SVT
in 217 infants concluded that medical treatment should continue for at least one year even after spontaneous resolution, suggesting that our management could have been further optimized. Whether the association of SVT with PHS we propose has a genetic basis or is secondary to structural defects in these patients, anesthesiologists should be prepared.

Our anesthetic management of this patient was successful because of preparation for further arrhythmias, and, once the diagnosis of PHS was made, because of preparation for difficult airway management with a fiberoptic bronchoscope if needed. Extra steps should be taken to confirm endotracheal placement under anesthesia when a misshapen epiglottis is encountered or when a diagnosis of PHS is suspected. We also propose that clinicians now beware of a possible association with SVT and PHS, requiring preparation with intravenous amiodarone or adenosine, pacer pads in place for anesthesia and transport, and possible direct current cardioversion.

**Figure 1**

![Shortened epiglottis of a 6-day-old infant with imperforate anus and polydactyly. Pallister-Hall syndrome (PHS) is a rare collection of such anomalies. This patient had a single atrium and episodes of supraventricular tachyarrhythmia, which have not been previously reported in a patient with PHS.]

**REFERENCES**


