ZOO ANIMALS

Tetralogy of Fallot in a red ruffed lemur (*Varecia rubra*)

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SUMMARY

A 3.5-month-old male 1.4 kg red ruffed lemur (*Varecia rubra*) was evaluated following auscultation of a grade IV/VI systolic cardiac murmur during routine neonatal examination. Echocardiography revealed a perimembranous ventricular septal defect (VSD), overriding (dextropositioned) aorta, right ventricular concentric hypertrophy and moderate pulmonic valve stenosis. There was right-to-left blood flow through the VSD. These findings are consistent with a tetralogy of Fallot with right-to-left shunting. Despite the poor prognosis associated with this disease, this patient has done relatively well for six years. To the authors' knowledge, this is the first published report of a tetralogy of Fallot in any lemur species.

CASE PRESENTATION

A 3.5-month-old male 1.4 kg red ruffed lemur (*Varecia rubra*) presented to the University of Illinois Zoological Medicine Service for evaluation of a grade IV/VI left pansystolic cardiac murmur that was initially detected during routine examination at one month of age. The lemur was born to a primiparous female in a litter of four. The affected lemur was noted to be approximately 20%–30% smaller in bodyweight at two months of age and appeared to spend more time on the ground than its littermates, with no apparent differences in appetite or fecal production. There was no evidence of breathlessness, dyspnoea or cyanosis reported by the husbandry staff. The lemur was housed in an 85.5 m^2 (920 sq. ft.) outdoor, fenced enclosure with multiple small wooden houses and ropes in a family group with both parents and three littermates. Physical examinations of the other lemur infants did not reveal any abnormalities. Before anaesthesia, the lemur was bright, alert, responsive and apprehensive. The patient was premedicated with 0.5 mg/kg butorphanol (Pfizer, New York, USA) and 0.5 mg/kg midazolam (West-ward, Eatontown, New Jersey, USA) by intramuscular injection while physically restrained. After approximately 30 min, the patient showed marked relaxation and induction was performed with 1.3 mg/kg etomidate (JHP Pharmaceuticals, Rochester, Michigan, USA) given intravenously to effect and an additional 0.5 mg/kg midazolam intravenously. The patient was then intubated, placed on 1.5%–2% isoflurane gas (MWI, Boise, Idaho ,USA) in oxygen and administered intravenous lactated Ringer's solution (Abbott Laboratories, North Chicago, Illinois, USA) at a rate of 10 mL/kg/hour. Lung sounds were monitored intermittently throughout the procedure to ensure no evidence of fluid overload was detected. Additionally, pulse oximetry was measured and remained at 100% throughout the procedure. Physical examination revealed a static grade IV/VI primarily left-sided pansystolic cardiac murmur and the mucous membranes appeared slightly cyanotic, although pigmentation limited full interpretation of this finding.

INVESTIGATIONS

Initial diagnostic testing included a complete blood count, venous blood gas, serum chemistry, spun packed cell volume, total solids and radiographs. Pertinent findings included normocythemia (red blood cell count $10.6\times10^6/\mu L$; reference range $6.30–11.35\times10^6/\mu L$;[1], hypernatraemia (155 mEq/L; reference range of 135–151 mEq/L), spun packed cell volume of high normal at 60% (reference range 35.2%–60.2%) and a low normal total protein of 6.0 g/dL (reference range 5.9–9.0 g/dL). Thoracic radiographs were unremarkable, including cardiac silhouette size, shape and position.

Echocardiogram using two-dimensional views and Doppler colour flow showed a 4-mm perimembranous ventricular septal defect (VSD) with right-to-left shunting of blood flow during systole at a velocity of approximately 1.5 m/s (Fig 1). Additionally, there was an overriding (dextropositioned) aorta and subjectively, there was concentric hypertrophy of the right ventricular wall, which was equal in thickness to the left ventricular free wall. The expectation based on small animal evaluation is that the right ventricular free wall should be no more than a third to half the thickness of the left.[2] Finally, spectral Doppler demonstrated moderate pulmonic stenosis, with a transpulmonic velocity of 3.6 m/s and an associated pressure gradient of 52 mmHg. Normal transpulmonic velocity is reported to be 0.95 m/s in brown lemurs (*Eulemur fulvus*) with a range of 0.6 m/s to 1.36 m/s.[3] These findings are consistent with a diagnosis of tetralogy of Fallot with right-to-left shunting.

OUTCOME AND FOLLOW-UP

Following recovery, the patient was returned to the family group. No noted clinical signs associated with the tetralogy of Fallot were identified for approximately two years. At that time, and again six months later, the patient presented with dull mentation and a wide, staggering gait. Bodyweight was 3.6 kg and grade IV/VI systolic murmur remained present on physical examination. Diagnostic testing

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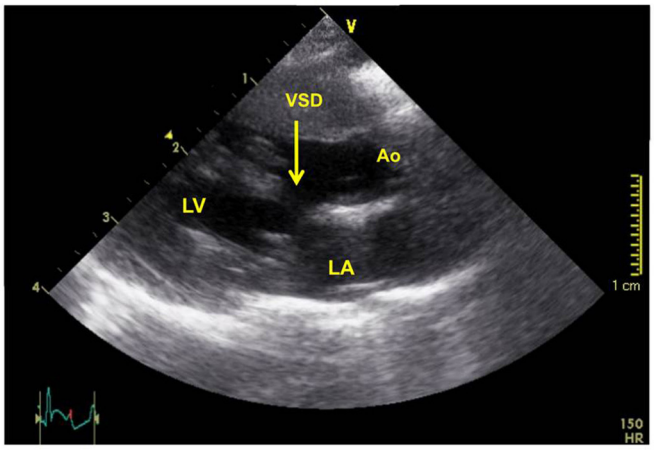

FIG 1: Echocardiographic image from a 3.5-month-old male red ruffed lemur (*Varecia rubra*) diagnosed with tetralogy of Fallot. Note the position of the aorta (Ao) over the large ventricular septal defect (VSD). LV, left ventricle, LA, left atrium.

included a repeat echocardiogram with findings that were unchanged from the previous exam. A complete blood count revealed erythrocytosis (red blood cell count $12.6\times10^6/\mu L$; reference range $6.30–11.35\times10^6/\mu L$;[1], with a mildly elevated haematocrit of 61.8% (reference range 35.2%–60.2%), and a normal total protein of 6.9 g/dL (reference range 5.9–9.0 g/dL). Ultimately the clinical signs were attributed to an infectious process, but it is unclear if the tetralogy of Fallot, or resultant erythrocytosis, contributed as well. Six years following tetralogy of Fallot diagnosis, the patient is apparently asymptomatic for cardiac disease and no further episodes have occurred.

DISCUSSION

Tetralogy of Fallot is a congenital cardiac defect consisting of a perimembranous VSD, an overriding (dextropositioned) aorta, pulmonic outflow tract stenosis and right ventricular concentric hypertrophy.[4] Right ventricular pressures can become elevated secondary to pulmonic stenosis, and can approach left ventricular (systemic) pressures causing reversal of flow with right-to-left shunting of blood through the VSD, as was seen in this case. This leads to deoxygenated blood mixing with oxygenated blood and an overall decrease in oxygen saturation within the systemic circulation. This decreased systemic oxygenation can trigger an increase in erythropoietin synthesis in the renal tissue, leading to erythrocytosis. In this patient, the noted erythrocytosis on follow-up examination is consistent with the right-to-left shunting noted on the echocardiogram. Erythrocytosis could also be indicative of dehydration, and this was a concern on the initial examination based on the high normal PCV. For this reason, fluids were administered at 10 mL/kg/hour even in this patient with cardiac disease to ensure appropriate renal perfusion during anaesthesia, but the lungs were ausculted frequently to monitor for fluid overload. However, signs of dehydration were not noted during physical assessment and total protein was within reference range, so this was retrospectively considered unlikely. Additionally, while the patient appeared to have a normocythemia on initial exam, young patients are often noted to have lower haematocrits than adults. The young age of this patient could have 'masked' a mild erythrocytosis at this time point as the reference values are compiled for all ages of red-ruffed lemurs.[1]

Clinical signs associated with tetralogy of Fallot include stunted growth, lethargy, exercise intolerance, weakness, respiratory distress, syncope and seizures.[4] Affected domestic and captive individuals have an advantage over their free-ranging counterparts due to the fact that they live in more controlled environments, have an overall lower risk of predation and do not need to aggressively forage for food. Despite right-to-left shunting, which increases the likelihood of severe complications associated with tetralogy of Fallot, this patient has shown no overt evidence of severe disease. This patient had evidence of cyanotic mucous membranes intermittently on physical examination. However, as noted above, there is pigmentation of the mucous membranes present in this species, which can impede use of membrane colour as a marker of oxygenation status.

Medical management of tetralogy of Fallot primarily consists of phlebotomy to ameliorate the clinical signs associated with erythrocytosis.[4] Surgical intervention to increase survivability and improve quality of life of patients with tetralogy of Fallot can be pursued. Surgical options include decreasing right-sided heart pressures by ballooning the stenotic area of the pulmonic outflow tract and repair of the VSD or by increasing the volume of oxygenated blood circulation through the pulmonary system by creating a systemic artery to pulmonary artery shunt.[4 5] These surgical options carry inherent risks and require cardiopulmonary bypass. No treatment has been deemed necessary in this patient to date based on the lack of clinical signs or worsening of condition. A recent retrospective study has shown that domestic dogs and cats with tetralogy of Fallot and no or low-grade heart murmurs had associated briefer median survival times.[6] That same publication reports an inverse relationship of the intensity of the systolic ejection murmur and severity of subvalvular obstruction in tetralogy of Fallot in human beings,[6] which represents a possible cause for the survival time difference noted in dogs and cats. Of note, the murmur in this patient is likely associated with the pulmonic stenosis, rather than the lower velocity flow through the VSD. Based on this information, a longer survival time is expected in this patient, as it has a grade IV/VI murmur. However, it remains a young adult, so vigilant monitoring for clinical signs is imperative as treatment may become indicated.

Tetralogy of Fallot has been reported in many species, including human beings, domestic canids, domestic felids, domestic equids, domestic bovids, a European brown bear (*Ursus arctos*), a Japanese macaque (*Macaca fuscata*), a ferret (*Mustelus putorius furo*) and a European beaver (*Castor fiber*).[4 7–14] Congenital heart disease is the most common congenital birth defect in human beings and the incidence is reported to be approximately 8 per 1000 live births, with the incidence of tetralogy of Fallot reported as 0.16–0.46 per 1000 live births.[10] A retrospective study of 151 dogs diagnosed with congenital heart disease showed only one case of tetralogy of Fallot, which constituted 0.6% of congenital heart defects in this study,[7] while a study evaluating 162 cats showed tetralogy of Fallot as 5% of cases with congenital heart disease.[14] The generally accepted proportion of tetralogy of Fallot within patients with congenital heart disease is approximately 5%–6% in domestic canids and felids.[4] To the authors' knowledge, this is the first report of tetralogy of Fallot in any lemur species, therefore no conclusions regarding incidence or prevalence can be formed.

Congenital heart disease has been shown in other species to have a primary genetic origin. In human beings, it is estimated that only 8%–12% of congenital heart disease can be attributed to environmental factors.[10] Genetic transmission of tetralogy of Fallot has been documented in keeshond dogs.[15] These facts raise

concern for the future breeding of this patient and continued breeding of its sire and dam. Red ruffed lemur is listed by the International Union for Conservation of Nature as a critically endangered species with a declining population.[16] Therefore, conservation of appropriate genetic diversity, as well as prevention of an effective genetic bottleneck that would potentially increase congenital disorders such as tetralogy of Fallot, are of increased importance in this species. Genetic analysis of this individual has not been pursued to date, but could be beneficial in determining future breeding recommendations for this species.

Although tetralogy of Fallot has been reported in many species, this is the first report in a lemur species. While this defect may be a genetic aberration that does not have lasting population effects, there is concern that this could represent a repeatable genetic impairment that could significantly impact an already declining population. The patient has recently left its family group to move to a new institution and, as of the date of publication, appears to be coping quite well with its cardiac defect. There are no plans for further treatment or diagnostic studies currently, however phlebotomy could be considered should clinical signs associated with erythrocytosis be noted.

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