Running head: Post-attenuation seizures in dogs with single cEHPSS

Title: Prognostic factors for short-term survival of dogs that experienced post-attenuation seizures following surgical correction of single congenital extrahepatic portosystemic shunts: 93 cases (2005-2018)

Authors:

Ronan A. Mullins, MVB[1]

Carlos Sanchez Villamil, DVM[1]

Laura E. Selmic, BVetMed (Hons), MPH, DACVS-SA, DECVS[2]

Mickey S. Tivers, BVSc(Hons), PhD, DECVS[3]

J. Brad Case, DVM, MS, DACVS[4]

Ameet Singh, BSc, DVM, DVSc, DACVS[5]

Kelley M. Thieman Mankin, DVM, MS, DACVS[6]

Davina Anderson, MA VetMB, PhD, DSAS(ST), DECVS[7]

Robert N. White, BSc(Hons), BVetMed, DSAS(ST), DECVS, SFHEA [8,9]

Kathryn M. Pratschke, MVB, MVM, DECVS[10]

Hilde de Rooster, DVM, MVM, PhD, DECVS[11]

Anne Kummeling, DVM, PhD, DECVS[12]

Donald A. Yool, BVMS, PhD, DECVS, SFHEA[13]

Melanie Olive, DVM[14]

Jean-Philippe Billet, Dr.vét, DECVS[14]

Ines Gordo, DVM, MS[15]

Herve Brissot, DEDV, DECVS[15]

Cameron Broome, BVSc(Hons), DVCS, FANZCVS[10]

Barbara M. Kirby, DVM, MS, DACVS, DECVS[1]

[1]Section of Veterinary Clinical Sciences, University College Dublin, Belfield, Dublin 4, Ireland.

[2]Department of Veterinary Clinical Sciences, The Ohio State University, 601 Vernon L Tharp St, Columbus, OH 43210.

[3]Bristol Veterinary School, University of Bristol, Langford House, Langford, Bristol BS40 5DU, UK.

[4]Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610.

[5]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Ontario, Canada.

[6]Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas, USA.

[7]Anderson Moores Veterinary Specialists, Poles Lane, Hursley, Winchester SO21 2LL, UK.

[8]Willows Veterinary Centre and Referral Service**,** Highlands Road, Shirley, Solihull, West Midlands B90 4NH, UK.

[9]School of Veterinary Medicine & Science, University of Nottingham, Sutton Bonington Campus, College Road, Loughborough LE12 5RD, UK.

[10]University of Glasgow, School of Veterinary Medicine, 464 Bearsden Rd, Bearsden, Glasgow G61 1QH, UK.

[11]Small Animal Department, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.

[12]Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands.

[13]The Royal (Dick) School of Veterinary Studies, Easter Bush Campus, Midlothian, Edinburgh EH25 9RG, UK.

[14]Centre Hospitalier Vétérinaire Atlantia, 22 Rue René Viviani, 44200 Nantes, France.

[15]Pride Veterinary Centre, Riverside Rd, Derby, Derbyshire, DE24 8HX, UK.

Corresponding author: Ronan A. Mullins, Section of Veterinary Clinical Sciences, University College Dublin, Dublin, Ireland. Email: ronan.mullins@ucd.ie

Abstract

Objective: To identify prognostic factors for short-term survival of dogs that experienced seizures within seven days following surgical correction of single congenital extrahepatic portosystemic shunts (cEHPSS).

Study Design: Multi-institutional retrospective study.

Sample Population: Ninety-three client-owned dogs.

Methods: Medical records at 14 veterinary institutions were reviewed to identify dogs that underwent surgical attenuation of a single cEHPSS from January 1st 2005 through February 28th 2018 and experienced post-attenuation seizures (PAS) within seven days postoperatively. Logistic regression analysis was performed to identify factors associated with one month survival. Factors investigated included participating institution, signalment, shunt morphology, concurrent/historical conditions, presence of preoperative neurologic signs, presence of preoperative seizures, aspects of preoperative medical management, surgical details including method and degree of shunt attenuation, type of PAS (focal only or generalized +/- focal), drugs administered as part of the treatment of PAS, and development of complications during treatment of PAS.

Results: Thirty (32.3%) dogs survived to 30 days. Seventy-six (81.7%) dogs experienced generalized PAS. Factors positively associated with short-term survival included having a history of preoperative seizures (p=0.004) and development of focal PAS only (p=0.0003). The majority of non-survivors were humanely euthanized due to uncontrolled or recurrent seizures.

Conclusions: Dogs that experienced PAS that had a history of preoperative seizures and those that experienced focal PAS only had significantly improved short-term survival.

Clinical Significance: The results of this study will help in the counseling of owners who seek treatment for PAS following surgical correction of cEHPSS.

Introduction

Development of post-attenuation seizures (PAS) is a well-recognized complication of surgical correction of portosystemic shunts in dogs,[1-25] with often fatal consequences.[1-3,8-10,12,15,18,21,22] These seizures have an incidence of up to 4.7-8.1% in the recent literature,[18,21,22,REDACTED] and occur almost exclusively within five days postoperatively.[1-25] The etiopathogenesis of PAS is not well understood. Proposed theories include a decline in systemic concentrations of endogenous benzodiazepines/benzodiazepine-like substances, hypoglycemia, electrolyte derangements (hypocalcemia and hypokalemia), hypoxemia, exacerbation of hepatic encephalopathy, an unknown perioperative metabolic event, sudden correction of an adapted to altered metabolic state, systemic hypertension, concurrent brain disease, intraoperative hypotension, and prolonged surgical and anesthetic times.[2,3,9,10,21,23,26,26] However; none of these has been consistently identified in previous studies.[1-25] For instance, PAS have been reported in the face of normal to only mildly elevated ammonia concentrations,[2,7,9,10,17,20,22] and normal glucose[7-10,17,20,21,23] and electrolyte concentrations.[17,20]

Large-scale studies investigating risk factors for PAS are lacking.[22] In a recent study by Strickland et al, increasing age and the presence of hepatic encephalopathy immediately preoperatively were identified as risk factors for postoperative neurologic signs and seizures.[22] Occurrence of PAS has not been definitively shown to be associated with shunt morphology (intra- or extrahepatic, or individual sub-morphologies), presence of preoperative seizures, or method or degree of shunt attenuation.[2,3,6,9,11,14-19,21,22] Certain breeds have been suggested as being at greater risk of PAS including Pugs,[6,9,23] Maltese terriers,[1,2] and Jack Russell terriers.[14]

On the basis of a limited number of case reports, small case series and isolated cases within retrospective studies, a guarded prognosis is typically provided following development of

PAS.[1-3,8-10,12,15,18,21,22] The largest published cohort of dogs affected by PAS is in a study by Strickland et al,[22] which described 12 dogs with PAS. In that study,[22] which included dogs with cEHPSS and cIHPSS, only seven of 12 dogs that experienced PAS survived to discharge. A number of studies; however, have reported a more favorable prognosis.[7,17,20,21] In one study,[21] dogs that experienced PAS that had a history of preoperative seizures demonstrated improved survival compared with those that had not. There are also reports of a more favorable outcome following treatment of PAS with administration of continuous rate infusion (CRI) of propofol.[7,17,20] A limitation of these reports; however, is their small size and the fact that other anti-epileptic drugs were administered concurrently with propofol CRI, which makes interpretation difficult.

The objective of this study was to identify prognostic factors for short-term survival of dogs that experienced PAS within seven days following surgical correction of single cEHPSS. We hypothesized that having received prophylactic LEV, treatment of PAS with propofol CRI, dogs that experienced PAS/underwent surgery in the second half of the study period, and development of focal PAS only would be positively associated with short-term survival.

Materials and Methods

Inclusion and exclusion criteria

Medical records at 14 institutions were retrospectively reviewed to identify dogs that underwent surgical attenuation (suture ligation [SL], thin film banding [TFB], or ameroid ring constrictor [ARC] placement) of a single cEHPSS from January 1st 2005 through February 28th 2018 and experienced PAS within seven days postoperatively. Exclusion criteria included dogs with cIHPSS, dogs that did not undergo shunt attenuation due to apparent concurrent portal vein aplasia; and dogs that were lost-to-follow-up prior to 30 days postoperatively. Dogs that experienced onset of seizure activity after seven days post-attenuation were excluded.

Data collection

Data retrieved from medical records of dogs that met inclusion criteria included breed, age, sex/neuter status, and bodyweight at surgery; year of surgery; shunt morphology (portocaval, portoazygous or portophrenic); concurrent/historical conditions at presentation; presence and type of preoperative neurologic signs and seizures; abnormal preoperative physical examination findings; method of shunt identification (abdominal ultrasound, computed tomography angiography [CTA], magnetic resonance imaging [MRI], intraoperative portovenography [IOPV], nuclear scintigraphy); details of preoperative medical management; prophylactic LEV or other anti-seizure medication(s); method- (SL, TFB or ARC) and degree (complete, partial, or none) of acute intraoperative shunt attenuation; timing and type of PAS (focal only or generalized +/- focal), electrolyte (sodium, potassium and chloride), glucose and ammonia concentrations around time of PAS occurrence; anti-seizure medication(s) administered as part of treatment of PAS; complications experienced during treatment of PAS; and whether the dog survived to one month. Regarding preoperative medical

169 management, dogs were recorded as having received at least one week's duration of
170 preoperative lactulose or not and at least one week's duration of antimicrobial(s) or not.
171 Preoperative diet type was also recorded. Dogs were divided into four groups concerning
172 prophylactic treatment with LEV: received no LEV (LEV-); received LEV at ≥20mg/kg
173 every eight hours (TID) for ≥24 hours preoperatively or 60mg/kg intravenous loading dose of
174 LEV perioperatively, and continued at ≥20mg/kg TID postoperatively (LEV1); received LEV
175 at <20mg/kg TID, for <24 hours preoperatively, or continued at <20mg/kg TID
176 postoperatively (LEV2); and received LEV postoperatively only (but prior to postoperative
177 seizure activity) according to the same preoperative protocol of group LEV1 (LEV3). Short-
178 term survival was defined as survival to 30 days. For dogs that did not survive to 30 days,
179 whether the dog had died naturally or been humanely euthanized and the cause/reason were
180 recorded. A complication was defined as any unanticipated event that altered the course of
181 PAS treatment.
182
183 **Statistical analyses**
184 Continuous variables were tested for normality using graphical methods, skewness, kurtosis
185 and Shapiro-Wilk tests. Normally and non-normally distributed continuous variables were
186 presented as mean and standard deviation (SD) and median and range, respectively. Categorical
187 variables were presented as frequency and percentages (with 95% CI). Comparison of
188 electrolyte, glucose and ammonia concentrations between survivors and non-survivors and
189 dogs with and without a history of preoperative seizures were made using the independent
190 samples t-test or Mann Whitney U-test depending on normality of the data. Univariable logistic
191 regression analysis was performed to assess for factor association with one month survival.
192 Factors assessed included contributing institution, breed, sex/neuter status, age, and
193 bodyweight at surgery; year of surgery; shunt morphology; presence of preoperative

neurological signs; presence of preoperative seizure activity; presence concurrent/historical conditions at presentation; whether the dog received a minimum of one week's duration of preoperative lactulose, whether the dog received a minimum of one week's duration of antimicrobial(s); LEV group (LEV-, LEV1, LEV2 or LEV3); method of shunt attenuation, degree of acute intraoperative shunt attenuation (complete, partial or none); whether the dog developed generalized or focal PAS only, and whether the dog experienced a complication during treatment of PAS. The second half of the study period was defined as January 1st 2012 onwards. Additional factors assessed included treatment of PAS with propofol CRI, alfaxalone CRI, benzodiazepine(s), LEV, phenobarbital, potassium bromide, alpha-2 agonist, gabapentin/pregabalin, flumazenil, and mannitol. Multivariable logistic regression analysis was performed to assess all variables identified with $p<0.2$ in the univariable analysis. Backwards selection was used with a retention alpha of 0.05 for variables to be retained in the model. This allowed calculation of adjusted odds ratios and 95% CI. The statistical analysis was performed using commercially available software.[a] Statistical significance was set at $p<0.05$.

Results

Ninety-three dogs were included in the study. Details of 75 dogs are the subject of another report.[REDACTED] Details of 16 dogs have partially been reported previously.[17,18,20,21]

Signalment

Breeds included mixed breed (n=18), Yorkshire terrier (n=15), Bichon Frise (n=12), Pug (n=9), Shih Tzu (n=8), Maltese terrier (n=6), Jack Russell terrier (n=6), Miniature Schnauzer (n=5), Chihuahua (n=4), Dachshund (n=3), West Highland white terrier (n=2), and one each of Norfolk terrier, Border terrier, Brussels Griffon, Coton De Tulear and Setter. There were 31 (33.3%) spayed females, 13 (14.0%) intact females, two (2.2%) unspecified females, 28 (30.1%) castrated males, and 19 (20.4%) intact males. Median (range) age was 34 (5-124) months. Median (range) weight was 6 (1.4-21.0) kg.

Year of surgery

Thirty-three (35.5%) dogs experienced PAS from January 2005 through December 2011 (first half of study period), 60 (64.5%) experienced PAS from January 2012 through February 2018.

Historical neurologic signs and seizures

Preoperative neurologic signs were recorded in 73/93 (78.5%) dogs. Preoperative seizures were recorded in 16/93 (17.2%) dogs. The most common neurologic signs included reduced mentation (n=46), pacing/wandering/compulsive walking (n=15), ataxia (n=12), abnormal behavior/behavior change (n=11), head pressing (n=9), hypersalivation/drooling (n=9), circling (n=8), disorientation (n=5), and four each of increased/inappropriate sleeping/sleepy, apparent blindness, and weakness.

Concurrent/historical conditions at presentation

Concurrent/historical conditions at presentation were recorded in 27/93 (29.0%) dogs and most commonly included urolithiasis (n=19); urinary tract infection (n=8); cardiac murmur (n=4); unspecified brachycephalic airway syndrome; and one each of urinary sediment/crystalluria, pattern baldness, distichiasis, and cryptorchidism. Two dogs had previously undergone cEHPSS attenuation, seven and 16 months prior, respectively, but did not experience PAS following initial surgery.

Method of shunt identification and morphology

Shunts were identified preoperatively by ultrasonography (n=75), CTA (n=31), nuclear scintigraphy (n=3), and/or MRI (n=1). Seventeen dogs underwent IOPV. Shunt morphology was available for 89/93 (95.7%) dogs and included portocaval (n=67), portoazygous (n=16), and portophrenic (n=6).

Preoperative medical management

Ninety-one (97.8%) dogs received preoperative medical management, which included combinations of antimicrobial(s), lactulose and a protein-restricted diet. One dog did not receive preoperative medical management. For the remaining dog, this information could not be confirmed. Seventy-eight (83.9%) dogs received at least one week of preoperative antimicrobial. Eighty-one (87.1%) dogs received at least one week of preoperative lactulose. Fifty-seven dogs received a prescription hepatic diet, eight received an unspecified protein-restricted diet, five received a protein-restricted renal diet. Other diets included a hypoallergenic diet (n=3), vegetarian diet (n=2), homemade protein-restricted diet (n=2), and one each received a gastrointestinal diet and homemade chicken and vegetable diet. For the remaining dogs, the type of diet was not recorded.

Prophylactic LEV or other anti-seizure medication(s)

Fifty (53.8%) dogs had received prophylactic LEV. One of these dogs had received additional prophylactic treatment with phenobarbital (3 mg/kg every 12 hours) and potassium bromide (8 mg/kg every 24 hours) for 3 months preoperatively. Forty-three (46.2%), 22 (23.7%), 25 (26.9%) and three (3.2%) dogs were included in groups LEV-, LEV1, LEV2 and LEV3, respectively.

Preoperative physical examination findings

Preoperative physical examination findings were available for 86/93 (92.5%) dogs. Abnormal findings were recorded in 48/86 (55.8%) dogs and most commonly included reduced/altered mentation/lethargy (n=22), underweight/suboptimal body condition (n=16), small stature (n=7), ataxia (n=6), circling (n=4), pacing/wandering (n=3), and cardiac murmur (n=3).

Method and degree of shunt attenuation

Shunts were attenuated using TFB (n=36, partial attenuation [n=20], no attenuation [n=16]); ARC (n=33, no attenuation [n=33]); SL (n=23, complete attenuation [n=20]; partial attenuation [n=3]); and combination of TFB and suture (n=1, partial attenuation [n=1]).

Type and timing of post-attenuation seizures

Seventy-six (81.7%) dogs were recorded as having developed generalized PAS, while 17 (18.3%) developed focal PAS only. Of the 76 dogs that experienced generalized PAS, 13 (17.1%) were recorded as having experienced focal PAS that later progressed to generalized despite treatment. Post-attenuation seizures commenced after a median (range) of 48 (3-144) hours postoperatively. Seventy-three (78.5%) dogs developed PAS while hospitalized. Twenty (21.5%) dogs displayed neurologic signs/commenced seizure activity post-discharge.

Electrolyte, glucose and ammonia concentrations at the time of post-attenuation seizures

Electrolyte, glucose and ammonia concentrations overall (when available), among survivors and non-survivors, and dogs with and without a history of preoperative seizures are listed in Table 1. No significant differences in these parameters were identified between survivors versus non-survivors or dogs with versus without a preoperative history of seizures (Table 1).

Treatment of post-attenuation seizures

Ninety (96.8%) dogs received treatment for PAS. One dog that experienced focal PAS only did not receive any anti-seizure treatment. A further dog that experienced focal PAS only did not receive any additional treatment apart from continued administration of LEV. One dog that experienced a generalized seizure at home was already receiving LEV but did not receive

any additional treatment. Specific details of drugs administered as part of the treatment of PAS were available for all but one dog. One dog that was receiving prophylactic LEV experienced generalized PAS treated by the primary veterinarian. Specific details regarding additional anti-seizure medication(s) administered were not available. Of 20 (21.5%) dogs that commenced seizure activity post-discharge, nine (45.0%; 9.7% of all dogs) were treated for PAS by their local veterinarian; eight (40.0%; 8.6% of all dogs) were re-presented to the participating institution; two (10.0%) were treated initially by the local veterinarian and subsequently re-presented; while the remaining dog was treated for generalized PAS with continued administration of LEV by the owner at home.

Focal seizures only

Dogs that experienced focal PAS only were treated with LEV (n=15; ten were already receiving prophylactic LEV; LEV1 [n=6], LEV2 [n=4]), benzodiazepine(s) (n=9), propofol CRI (n=6), phenobarbital (n=6), potassium bromide (n=3), flumazenil (n=2), alpha-2 agonist (n=1), and/or gabapentin (n=1). One dog was taken back to surgery to have the thin film band removed due to concerns over possible portal hypertension; moderate liver congestion was noted at surgery but without congestion of mesenteric vessels. The dog was euthanized intraoperatively at the request of the owners.

Generalized seizures

Dogs that experienced generalized PAS were treated with LEV (n=49; 34 were already receiving prophylactic LEV; LEV1 [n=16], LEV2 [n=21], LEV3 [n=3]), phenobarbital (n=49; one dog was already receiving prophylactic phenobarbital), propofol CRI (n=43), benzodiazepine(s) (n=36), mannitol (n=16), potassium bromide (n=10; one dog was already

receiving prophylactic potassium bromide), alpha-2 agonist (n=7), alfaxalone CRI (n=3), and/or gabapentin/pregabalin (n=3).

Development of complications during treatment of post-attenuation seizures

Sixteen (17.2%) dogs experienced one or more significant complication(s) during treatment of PAS within 30 days postoperatively (Table 5). The most common complication was development of aspiration pneumonia.

Short-term survival

Thirty (32.3%) dogs survived to 30 days. Of those that did not survive, 50 (79.4%) were humanely euthanized, nine (14.3%) died, one (1.6%) suffered cardiorespiratory arrest and was successfully resuscitated but later euthanized. For the remaining three (4.8%) dogs, it was not recorded whether they had died or been euthanized. The most common reason for euthanasia was uncontrolled or recurrent seizures (Table 5). Median (range) survival time of non-survivors was 4 (1-20) days (recorded as 2-3 weeks postoperatively [n=1]). Of those that survived to 30 days, 16 experienced generalized PAS, 14 experienced focal PAS only. Sixty dogs that did not survive to 30 days experienced generalized PAS, while three experienced focal PAS only. Cause of natural death and reasons for humane euthanasia are listed in Table 5.

Prognostic factors associated with short-term survival

Results of univariable analysis are summarized in Tables 2 and 3. Prophylactic treatment with LEV, surgery performed in the second half of the study period, and treatment of PAS with propofol CRI were not associated with short-term survival. Factors associated with short-term survival in the multivariable analysis included having a history of preoperative seizures

(p=0.004) and type of PAS (p=0.0003) (Table 4). Dogs with a history of preoperative seizures had a 7.6-fold (95% CI: 1.9-30.3) increased odds of survival to 30 days compared with those without, with adjustment for PAS type. Dogs that developed focal PAS only had significantly increased odds of survival (OR=14.4 (95% CI: 3.4-60.2)) compared with those that experienced generalized PAS, with adjustment for preoperative seizure activity.

Discussion

The main findings of this study are: (1) affected dogs that had a history of preoperative seizures and those that experienced focal PAS only had significantly increased odds of survival to 30 days, and (2) having received prophylactic treatment with LEV, treatment of PAS with propofol CRI, and having undergone surgery/experienced PAS in the second half of the study period were not associated with improved short-term survival.

In a recent study by Brunson et al,[21] dogs that experienced PAS that had a history of preoperative seizure activity had a 7-fold increased probability of survival compared with those that had not. Similarly, in our study, such dogs had an almost 8-fold increased odds of survival to 30 days. One possible explanation for this is that PAS experienced by both of these subsets of dogs have a different etiopathogenesis or that some dogs with a history of preoperative seizure activity have continuation of these seizures postoperatively. We did not find support for hyperammonemia to be responsible for PAS in such affected dogs in our study, which is consistent with reports by several other investigators.[2,7,9,10,17,20,22] It is well recognized that ammonia concentrations and severity of encephalopathy do not always correlate, emphasizing the importance of other neurotoxic substances.[27] In a study by Strickland et al,[22] the presence of hepatic encephalopathy immediately preoperatively was identified as a risk factor for PAS; however, similar to our results, postoperative ammonia concentrations were normal to mildly elevated in all dogs for whom it was available.

Dogs that experienced focal PAS only in our study had 14.4-fold increased odds of short-term survival compared with those that experienced generalized PAS. Whether focal PAS in such affected dogs represent a less aggressive form of neurologic dysfunction, has a different etiopathogenesis, or would have progressed to generalized PAS without anti-seizure treatment

392 is unknown. Seventeen percent of dogs that developed generalized PAS in our study were
393 recorded as having experienced initial focal PAS, which highlights that these may be a
394 precursor to generalized PAS in some cases. In a study by Mehl et al,[15] all dogs that experienced
395 focal PAS only survived to discharge, while all those that experienced generalized PAS within
396 seven days postoperatively died during hospitalization. The majority of dogs that failed to
397 survive to 30 days in our study were humanely euthanized, most commonly due to uncontrolled
398 or recurrent seizures (Table 5). It is possible that factors such as client unwillingness to continue
399 treatment, financial constraints, or an attending clinician's perception of a poor prognosis for
400 neurologic recovery may have significantly influenced the decision to euthanize. It may be
401 anticipated that generalized PAS may be more challenging to abolish, more distressing for the
402 pet owner to observe, associated with a greater treatment cost and the perception of a poorer
403 prognosis for recovery, all of which may provoke a decision to euthanize.
404
405 Only one third of dogs that experienced PAS in our study survived to 30 days, which is in
406 agreement with previous reports of 0-53.8% in the literature.[2,3,9,15,18,21,22] The large proportion
407 (81.7%) of dogs in our study that experienced generalized PAS will have strongly influenced
408 the low short-term survival rate as such dogs had significantly decreased odds of survival in
409 the multivariable analysis.
410
411 We hypothesized that having undergone surgery/experienced PAS in the second half of the
412 study period would be positively associated with short-term survival. This was based on the
413 premise that with greater experience in treating PAS and advances in critical care medicine,
414 short-term survival would be improved. This was not supported by the results of our study.
415 Possible explanations for this may be related to factors such as a perceived poor prognosis for
416 neurologic recovery, factors outside of the control of the attending clinician including client

417 unwillingness to pursue treatment and financial constraints, and the overall infrequent
418 occurrence of PAS. In our study, the maximum number of cases of PAS seen by any institution
419 in a single year was four, with most institutions seeing a maximum of one to two cases per
420 year.
421
422 Administration of several anti-epileptic drugs has been described for the treatment of PAS in
423 previous reports including benzodiazepines,[2,3,9-12,14,15] barbiturates,[2,3,6-12,14,15] and
424 propofol.[7,10,14,17] There are; however, no large-scale studies which compare outcomes of
425 affected dogs treated with various anti-epileptic drugs, likely due to the infrequent occurrence
426 of these seizures and subsequent small case numbers within individual institutions.[22] In our
427 study, none of these anti-epileptic drugs, including propofol CRI, was associated with short-
428 term survival. On the basis of its non-prospective nature, treatment of PAS with propofol CRI
429 was not randomized in our study. Therefore, it is likely that it will have been administered to
430 the most severely affected cases in our study. While there are reports of a more favorable
431 prognosis with administration of propofol CRI,[7,17,20] individual numbers are small and may
432 represent a positive outcome publication bias. Previous studies have reported conflicting results
433 regarding the possible protective effect of LEV against development of PAS.[18,21,22,REDACTED]
434 Approximately half of the dogs in our study received prophylactic LEV. The recommended
435 dose of LEV is 20 mg/kg *per os* every eight hours for a minimum of 24 hours preoperatively.[27]
436 On the basis of the known pharmacokinetics of the drug (albeit in healthy dogs), continuation
437 of the drug at the same dose during the first seven days postoperatively should be considered.[28]
438 Several dogs in our study received less standardized protocols of LEV (groups LEV2 and
439 LEV3). No group; however, was of prognostic significance. It is possible that dogs that develop
440 PAS despite receiving prophylactic treatment with LEV are biased toward more severe post-
441 attenuation neurologic dysfunction, although this is purely speculative. It also raises the

question whether continued treatment of such dogs with LEV following development of PAS is likely to be of benefit.

This study has a number of important limitations. Like all retrospective studies, the accuracy of the presented data relies on the completeness of the medical records. Seventy-five of the dogs of the present report are the subject of another study which investigated the effect of prophylactic treatment with LEV on the incidence of PAS in dogs that underwent cEHPSS attenuation.[REDACTED] On the basis of the infrequent occurrence of PAS, the present study would not have been possible without the inclusion of such dogs. This was a multicenter study involving multiple surgeons, with differences in case management and experience in treating PAS. Treatment of PAS with different anti-epileptic drugs was not randomized but rather based on clinician preference. Drug dosages and infusion dose rates were not standardized. We did not record individual doses of various anti-epileptic drugs used to treat PAS as these will have varied widely even within individual dogs, with most dogs receiving numerous boluses of individual drugs along with variable rates of CRIs. Other factors including the attending clinician's perception of prognosis for neurologic recovery following development of PAS, the extent to which the seizures were treated, cost of treatment and client willingness to treat seizures cannot be controlled due to the retrospective nature of the study. The authors acknowledge that several of the dogs included in this study may have experienced prodromal neurologic signs prior to seizure onset; however, due to its retrospective nature, the exact timing and details of such may not have been accurately recorded in the medical record. The classification of seizures as focal or generalized in this study reflects what was recorded in the medical record. Assignment of a dog as having experienced a seizure will have been based on the attending clinician's/criticalist's interpretation of the neurologic signs manifested. Importantly; however, all dogs were treated

at academic teaching hospitals or referral institutions, by multidisciplinary staff with extensive experience in treating dogs with portosystemic shunts and their complications. Finally, just under 10% of dogs that experienced PAS in this study were not treated for PAS at the operating institution and the impact of this on the survival of such dogs is unknown.

The overall short-term survival rate in this study was low, with just under one third of dogs surviving to 30 days. Affected dogs that had a history of preoperative seizures or experienced focal PAS only had significantly improved short-term survival. The results of this study will help in the counseling of owners who seek treatment for cEHPSS and may serve as a basis for further investigation regarding prevention or treatment of PAS in the future.

Disclosure Statement

The authors report no conflict of interest.

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Footnotes

[a]SAS version 9.4, SAS institute, Cary, NC.

611 **Table 1:** Electrolyte, ammonia and glucose concentrations of all affected dogs (with results
612 available), survivors and non-survivors, and dogs with and without a history of preoperative
613 seizures.

614 **Abbreviations:** SD; standard deviation.

Parameter	**Overall (n=93)**	**Survivors (n=30)**	**Non-survivors (n=63)**	**P-value**	**History of preoperative seizure activity (n=16)**	**No history of preoperative seizure activity (n=77)**	**P-value**
Sodium Median (range)	143.5 (135.1-171.0) (n=44) Recorded as normal (n=3)	144.0 (137.0-155.0) (n=17)	142.5 (135.1-171.0) (n=27)	0.81	144.4 (137-151.4) (n=11)	143.0 (135.1-171.0) (n=33)	0.44
Potassium Mean (±SD)	4.0 (±0.4) (n=44) Recorded as	4.1 (±0.5) (n=17)	4.0 (±0.4) (n=27)	0.69	4.1 (±0.7) (n=11)	4.0 (±0.3) (n=33)	0.82

	normal (n=3)						
Chloride Mean (±SD)	114.4 (±6.2) (n=33) Recorded as normal (n=2) Recorded as high (n=1)	114.6 (±3.5) (n=14)	114.2 (±7.7) (n=19)	0.81	115.1 (±4.8) (n=8)	114.1 (+6.7) (n=25)	0.70
Ammonia Median (range)	32.3 (0.0-261.6) (n=38) Recorded as within normal limits (n=6) Recorded as high (n=1)	28.8 (5.0-93.0) (n=14)	39.5 (0.0-261.6) (n=24)	0.35	46.0 (13.0-104.0) (n=6)	32.3 (0.0-261.6) (n=32)	0.60

Glucose Median (range)	5.3 (1.1-11.1) (n=50) Recorded as normal (n=2)	5.5 (2.4-7.2) (n=20)	5.2 (1.1-11.1) (n=30)	0.40	5.8 (3.9-7.2) (n=10)	5.2 (1.1-11.1) (n=40)	0.13

615

616 **Table 2:** Results of univariable regression analysis of variables potentially associated with
617 survival to 30 days.

618 **Abbreviations:** LEV; levetiracetam.

Variable	**Category**	**n,**	**%**	**Survivors (n)**	**Non-survivors (n)**	**P value**
Center						0.48
Breed	Mixed breed	18	19.4	4	18	0.98
	Yorkshire terrier	15	16.1	7	8	
	Bichon Frise	12	12.9	6	6	
	Shih Tzu	8	8.6	1	7	
	Maltese terrier	6	6.5	1	5	
	Pug	9	9.7	3	6	

	Miniature Schnauzer	5	5.4	2	3	
	Jack Russell terrier	6	6.5	2	4	
	Dachshund	3	3.2	0	3	
	Chihuahua	4	4.3	1	3	
	West Highland White terrier	2	2.2	1	1	
	Norfolk terrier	1	1.1	1	0	
	Border terrier	1	1.1	1	0	
	Brussels Griffon	1	1.1	0	1	
	Coton De Tulear	1	1.1	0	1	
	Setter	1	1.1	0	1	
Sex	Male entire	19	20.4	6	13	0.64
	Male neutered	28	30.1	6	22	
	Female entire	13	14.0	5	8	
	Female spayed	31	33.3	12	19	
	Unspecified female	2	2.2	1	1	

Age (months)	Median (range)	34	(5-124)	34.5 (5-64)	34 (6-124)	0.15
Weight (kg)	Median (range)	6	(1.4-21.0)	6.0 (1.4-8.9)	6.0 (1.8-21.0)	0.16
Shunt morphology	Portocaval	67	72.0	24	43	0.99
	Portoazygous	16	17.2	6	10	
	Portophrenic	6	6.5	0	6	
	Unspecified	4	4.3	0	4	
Concurrent/historical conditions	Yes	27	29.0	9	18	0.89
	No	66	71.0	21	45	
Preoperative neurologic signs	Yes	73	78.5	27	46	0.07
	No	20	21.5	3	17	

Preoperative seizures	Yes	16	17.2	12	4	0.0003
	No	77	82.8	18	59	
Preoperative antimicrobial(s) for minimum of one week	Yes	78	83.9	29	49	0.18
	No	13	13.9	1	12	
	Unknown	2	2.2	0	2	
Preoperative lactulose for minimum of one week	Yes	81	87.1	30	51	0.99
	No	10	10.7	0	10	
	Unknown	2	2.2	0	2	
Prophylactic LEV	LEV-	43	46.2	15	28	0.2
	LEV1	22	23.7	10	12	

	LEV2	25	26.9	4	21	
	LEV3	3	3.2	1	2	
Year of surgery	2005	2	2.2	0	2	0.94
	2006	3	3.2	2	1	
	2007	1	1.1	0	1	
	2008	5	5.4	1	4	
	2009	2	2.2	0	2	
	2010	10	10.8	6	4	
	2011	10	10.8	3	7	
	2012	14	15.1	5	9	
	2013	12	12.9	4	8	
	2014	6	6.5	1	5	
	2015	12	12.9	3	9	
	2016	12	12.9	3	9	
	2017	3	3.2	1	2	

	2018	1	1.1	1	0	
Surgery from January 1st 2012 onwards	Yes	60	64.5	18	42	0.53
	No	33	35.5	12	21	
Method of shunt attenuation	Suture ligation	23	24.7	6	17	0.52
	Thin film banding	36	38.7	10	26	
	Ameroid ring constrictor	33	35.5	14	19	
	Suture ligation and thin film banding	1	1.1	0	1	
Degree of intraoperative attenuation	None	49	52.7	17	32	0.87
	Partial	24	25.8	7	17	
	Complete	20	21.5	6	14	

Type of seizures	Generalized	76	81.7	16	60	<0.0001
	Focal only	17	18.3	14	3	

619

620 **Table 3:** Results of univariable analysis of drugs administered as part of treatment of PAS.

621 **Abbreviations:** CRI: continuous rate infusion.

Variable	**Category**	**n,**	**%**	**Survivors (n)**	**Non-survivors (n)**	**P value**
Propofol CRI	Yes	49	52.7	12	37	0.21
	No	43	46.2	18	25	
	Unknown	1	1.1	0	1	
Alfaxalone CRI	Yes	3	3.2	0	3	1.0
	No	89	95.7	30	59	
	Unknown	1	1.1	0	1	
Mannitol	Yes	16	17.2	3	13	0.44
	No	76	81.7	27	49	
	Unknown	1	1.1	0	1	
Benzodiazepine(s)	Yes	45	48.4	11	34	0.27
	No	47	50.5	19	28	

	Unknown	1	1.1	0	1	
Levetiracetam	Yes	64	68.8	22	42	0.52
	No	29	31.2	8	21	
Phenobarbital	Yes	55	59.1	16	39	0.68
	No	37	39.8	14	23	
	Unknown	1	1.1	0	1	
Potassium bromide	Yes	13	14.0	7	6	0.23
	No	79	85.0	23	56	
	Unknown	1	1.1	0	1	
Alpha-2 agonist	Yes	8	8.6	4	4	0.56
	No	84	90.3	26	58	
	Unknown	1	1.1	0	1	
Gabapentin/pregabalin	Yes	4	4.3	2	2	0.45
	No	88	94.6	28	60	
	Unknown	1	1.1	0	1	
Flumazenil	Yes	2	2.2	2	0	0.98
	No	91	97.8	28	63	
	Unknown	1	1.1	0	1	

Complication during treatment of post-attenuation seizures	Yes	16	17.2	2	14	0.08
	No	77	82.8	28	49	

Table 4: Results of multivariable logistic regression model assessing relationship with outcome of survival to 30 days.

Variable	Category	Odds Ratio	95% CI	P-value
Preoperative seizures	Yes	7.6	1.9-30.3	0.004
	No	Ref		
Type of PAS	Focal only	14.4	3.4-60.2	0.0003
	Generalized +/- focal	Ref		

Table 5: Reason for euthanasia, cause of natural death and complications during treatment of post-attenuation seizures. *Not recorded if died or euthanized (n=3), †Not recorded if died or euthanized (n=3).

Cause of natural death*	▪ Cardiorespiratory arrest (n=5) ▪ Aspiration pneumonia (n=1) ▪ Suspect cerebrocortical necrosis secondary to severe hypernatremia and hyperchloremia (n=1) ▪ Spontaneous death (n=1)

	▪ Heart failure, pulmonary edema (n=1)
Reason for euthanasia†	▪ Uncontrolled or recurrent seizures (n=24) ▪ Persistent seizures and poor prognosis (n=8) ▪ Uncontrolled seizures +/- financial limitations to ascertain if seizures would eventually cease (n=5) ▪ Respiratory arrest (n=2) ▪ Poor mentation (n=1) ▪ Blind, unable to stand, welfare concerns (n=1) ▪ Disorientated, vocalizing and non-responsive (n=1) ▪ Seizures, suspected aspiration pneumonia (n=1) ▪ Seizures, hypoventilation and poor prognosis (n=1) ▪ Seizures, unresponsive and fulminant liver failure (n=1) ▪ Suspected portal hypertension (n=1) ▪ Aspiration pneumonia (n=1) ▪ Uncontrolled neurologic signs (n=1) ▪ Uncontrolled seizures and pulmonary edema (n=1) ▪ Unsuccessful reanimation (n=1) ▪ Seizures, coma (n=1)
Complications during treatment of post-attenuation seizures	▪ Aspiration pneumonia (n=4) ▪ Pyrexia, respiratory arrest and aspiration pneumonia (n=1) ▪ Aspiration pneumonia and suspect thromboembolic event (n=1)

	▪ Acute renal failure, cardiogenic edema and pneumonia (n=1) ▪ Repeated respiratory arrest (n=1) ▪ Hypoventilation requiring mechanical ventilation (n=1) ▪ Hypoventilation requiring mechanical ventilation, suspected vagal event (hypertension and tachycardia), respiratory arrest (n=1) ▪ Fulminant liver failure (n=1) ▪ Hyperthermia, tachycardia, hematochezia suspected related to portal hypertension (no mesenteric congestion at revision coeliotomy) (n=1) ▪ Sepsis suspected to be associated with gastrostomy tube (n=1) ▪ Sepsis, systemic inflammatory response syndrome, disseminated intravascular coagulation, suspect pneumonia, requirement for mechanical ventilation (n=1) ▪ Pulmonary edema (n=1) ▪ Pulmonary edema, hypothermia and hyperthermia (n=1)

629