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Incidence and Risk Factors for Post-Attenuation Neurological Signs in 253 Dogs with a Single Congenital Portosystemic Shunt

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Abstract

Objective

To describe the incidence, outcome and identify possible risk factors for Post Attenuation Neurological Signs (PANS) and seizures in dogs that have undergone attenuation of a single congenital portosystemic shunt (CPSS).

Study Design

Retrospective cohort study.

Sample Population

Dogs (n=253) with a single, congenital portosystemic shunt.

Methods

Medical records of dogs with a single CPSS surgically attenuated between February 2000 and July 2015 were reviewed for signalment, pre and post-operative clinical data, including the occurrence of PANS. Univariable and multivariable binary logistic regression was used to assess risk factors for PANS and for seizures.

Results

Twenty eight (11.1%) dogs developed PANS, including twelve (4.7%) dogs that seizured. Five (17.9%) dogs with PANS did not survive to discharge.

The risk factors for PANS included the presence of HE immediately pre-operatively ($p=0.038$, odds ratio 2.704, confidence interval 1.057-6.922) and increasing age ($p<0.001$, odds ratio 1.476, confidence interval 1.223-1.780). The risk factors for seizures included the presence of HE immediately pre-operatively ($p=0.048$, odds ratio 3.538,

23 confidence interval 1.013-12.363) and increasing age (p=0.009, odds ratio 1.364,
24 confidence interval 1.082-1.720).
25
26 **Conclusions**
27 Pre-operative HE and older age in dogs with a CPSS increase the odds of developing
28 PANS and seizures. Neither extrahepatic or intrahepatic shunts were at an increased risk
29 of developing PANS or seizures. Prophylactic levitiracetam was not protective for the
30 development of PANS or seizures.
31
32 **Clinical Significance**
33 Our findings would suggest that surgical attenuation of a single CPSS should not be
34 excessively delayed and that clinical signs of HE should be stabilized before surgery.

Introduction

Post Attenuation Neurological Signs (PANS) are a complication of the surgical management of Congenital Portosystemic Shunts (CPSS) reported in up to 12% of dogs.[1–7] Signs vary from mild ataxia [2,8] to generalized seizure activity. [5,6,9] PANS is a well recognised complication in dogs, however, the underlying aetiology is unclear and may be linked to changes associated with hepatic encephalopathy (HE) prior to surgery. [6,9]

Dogs with CPSS often show signs of HE, a poorly understood syndrome of neurological signs caused by alterations of multiple factors including ammonia and false neurotransmitters.[10–12] In dogs with CPSS, ammonia and inflammatory mediators predict the presence of HE[13] and indicators of inflammation reduce following successful CPSS attenuation.[14] HE is commonly observed in people secondary to a variety of liver diseases, however the pathogenesis remains unclear.

HE may cause chronic alterations in the central nervous system[15–19] and there is direct evidence of astrocyte alterations in the brains of dogs with CPSS. [10,21] It is hypothesised that the central nervous system becomes adapted to an abnormal metabolic environment pre-operatively and a sudden change to this favours an excitatory state.[2] Alternatively, damage to the CNS as a result of chronic portosystemic shunting, coupled with a metabolic event post attenuation could result in PANS.[6]

PANS is recognised to be a separate entity to HE,[1] occurring even when the CPSS is fully attenuated at surgery.[22,23] In one study all animals affected with PANS had normal levels of ammonia,[24] whereas HE is commonly associated with hyperammonaemia.[13]

Increasing age has been associated with PANS in some studies [2,6,9], but not others.[25,26] There is conflicting evidence about whether dogs with extrahepatic shunts carry an increased risk of developing PANS, and the effect of the method or degree of shunt attenuation is unknown.[2,4,23,25,27]

Changes in sodium affect osmolality. Central pontine myelinolysis is one of the most severe causes of post-operative neurological signs in people undergoing orthotopic liver transplantation and is associated with rapid correction of hyponatraemia.[28] In addition a reduction of osmolality is associated with increased risk of seizures in people and other animals.[19,29]

Administration of prophylactic anti-seizure medication to dogs with CPSS in the peri-operative period has shown mixed results. Peri-operative levetiracetam seemed to reduce the incidence of post-operative seizures in one retrospective study,[3] whereas phenobarbitone potentially reduced the severity, but not the incidence of neurological dysfunction in another.[2]

79 The aim of the current study was to retrospectively review the records of dogs that had
80 undergone surgical attenuation of a single CPSS, to describe the incidence, outcome and
81 identify risk factors for PANS and seizures. We hypothesised that age, the presence of
82 HE pre-surgery, extrahepatic shunt morphology and alterations in osmolality post-
83 operatively would be significantly associated with the incidence of PANS and seizures.
84 Additionally, we hypothesised that peri-operative administration of levetiracetam would
85 not affect the incidence of PANS or seizures.

Materials and Methods

The records of dogs that underwent surgery for the attenuation of a single congenital portosystemic shunt at our institution between February 2000 and July 2015 were reviewed. Diagnosis of a single CPSS was confirmed at surgery with a mesenteric portovenogram in all cases.[30] The details recorded were signalment, bodyweight, duration of clinical signs related to a CPSS, (neurological, urinary and gastrointestinal), severity and duration of HE prior to surgery, response to medical treatment prior to surgery, pre-surgery serum albumin, pre and 24hr post-operative plasma ammonia, peri-operative levetiracetam, shunt type (intrahepatic or extrahepatic), method of attenuation and the degree of attenuation achieved, post-operative serum osmolality at three time points, the nature, timing and outcome of any complications related to PANS and the number of days hospitalisation. Ammonia was measured using a Stasar III Spectrophotometer (Gilford Instrument Laboratories Incorporated, Ohio, USA) or a Jenway 6310 Spectrophotometer (Bibby Scientific Limited, Staffordshire, UK). Albumin was measured using a ILab 600 clinical chemistry analyser (Instrumentation Labaratory, Werfen, Warrington, UK).

Electrolytes, urea (BUN) and glucose were measured using a blood gas analyser. Osmolality was calculated by the blood gas analyser using the following formula: $Osm(mOsm/kg) = 1.86[Na^+] + ([Glu]/18) + ([BUN]/2.8) + 9$. The same blood gas, electrolyte and metabolite analyser was used for individual dogs, but three analysers were used over the study period (<2003 IRMA TRUpoint^R, LifeHealth UK; 2003-2011 Stat

Profile^{R} Critical Care Xpress, Nova Biomedical UK; >2011 Stat Profile^{R} pHOx^{R} Ultra, Nova Biomedical UK).

HE before the commencement of medical management (Table 1) and immediately pre-operatively (Table 2) was graded. Dogs were deemed to have PANS if any neurological signs were noted after surgery and before discharge. PANS were graded as mild, moderate or severe (Table 3). Dogs underwent CPSS attenuation according to a standardized surgical protocol.[25,30] The anaesthesia protocol was at the discretion of the anaesthetist. As previously reported, the decision to partially or completely attenuate the CPSS was made on the basis of portal pressure measured via mesenteric vein catheterization and visual assessment of the pancreas and intestinal tract for signs of portal hypertension. Dogs that could tolerate a complete attenuation were treated with a complete acute suture ligation, those that could not were treated either with a partial suture ligation or a cellophane band.[30]

Statistical analysis was performed using the statistical software package IBM SPSS Statistics 23.0.0 (SPSS (UK) Limited IBM, Woking, UK). Data were assessed graphically for normality. Median and range are reported for non-normally distributed variables. Categorical data are reported as percentages. The pre-operative and post-operative levels of plasma ammonia were compared using the Wilcoxon Signed Rank Test. Statistical significance was set $P \leq 0.05$.

Univariable binary logistic regression was performed using each potential predictor variable (Tables 5 and 6) as an initial screening to identify possible risk factors for PANS and seizures for use in multivariable models.

Variables were selected for univariable binary logistic regression that had been previously associated with outcome or were related to the study hypothesis.[2,3,6,13,19,31] Multivariable binary logistic regression models were then developed initially using the variables with a $P \leq 0.10$ in the univariable analysis. Variables were sequentially entered into the logistic regression model and retained if $P \leq 0.05$. Once the model was finalized, excluded variables were re-assessed by individually re-entering them back into the model. Two models were created, one for PANS and one for seizures.

Correlation between variables used in the multivariable analysis was assessed using a Spearman's Rank Correlation.

Results

Two hundred and fifty-three dogs with a single CPSS were included in the study. Three other cases were omitted due to incomplete medical records. Where dogs had more than one surgery only the details of the first surgery were included. One hundred and thirty-seven dogs (54.2%) were male and 116 dogs (45.8%) were female. One hundred and seventy-five dogs (69.2%) were intact and 78 dogs (30.8%) were neutered. The median age at time of surgery was 0.87 years (range 0.20-11.98). The median weight at surgery was 6.3kg (range 1.0-50.0).

The median duration of clinical signs prior to surgery was 57 days (range 5-1436). HE grade prior to medical management was 1 in 71 dogs (28.1%), 2 in 108 dogs (42.7%), 3 in 72 dogs (28.5%) and 4 in two dogs (0.8%). Two hundred and thirty-eight dogs (94.1%) were treated with medical management prior to surgery and 15 dogs (5.9%) did not receive any treatment. Of the 238 dogs that had medical management prior to surgery there was a good response in 176 dogs (73.9%), a moderate response in 49 dogs (20.6%) and a poor response in 13 (5.5%). The HE grade following medical management was grade 1 in 196 dogs (82.4%), grade 2 in 37 dogs (15.5%), grade 3 in four dogs (1.7%) and grade 4 in one dog (0.4%). The median duration of medical management prior to surgery was 23 days (range 0-730).

One hundred and ninety-six dogs (77.5%) had an extrahepatic CPSS and 57 dogs (22.5%) had an intrahepatic CPSS. One hundred and forty-eight dogs (58.5%) were able to tolerate a partial attenuation and 105 dogs (41.5%) were able to tolerate a complete

attenuation. Of the 148 dogs treated with a partial attenuation 12 (8.1%) were treated with a cellophane band, the remainder with partial suture ligation.

Fifty-four dogs (21.3%) received peri-operative levetiracetam 20mg/kg orally every 8 hours for a minimum of 24 hours pre-operatively and a minimum of five days post-operatively. Dogs may have received levetiracetam for longer if prescribed by the referring veterinary surgeon.

Serum albumin was measured pre-operatively in 227 dogs (89.7%). The median albumin was 26.2g/l (range 7.9-35.8g/l), the reference range 49-71g/l.

Plasma ammonia was measured in 186 dogs (73.5%) pre-operatively. The median ammonia concentration was 163.0µmol/l (range 8-590), reference range 0-70µmol/l. Post-operative ammonia was measured in 119 dogs with a median of 82µmol/l (range 13-677). Paired pre and post-operative ammonia samples were available for 104 dogs (41.1%). There was a statistically significant decrease in ammonia after surgery from a median of 147.5µmol/l (range 8-544) to a median of 80.0µmol/l (range 13-677) ($p<0.001$).

Twelve dogs (4.74%) did not survive to discharge, seven of these dogs died or were euthanized for reasons not related to PANS. Three dogs died or were euthanized due to severe gastrointestinal haemorrhage, one dog due to suspected portal hypertension and pulmonary thromboembolism, one dog due to severe anaemia secondary to a

coagulopathy, one dog due to a portal vein thrombus and one dog due to postoperative intussusception.

Twenty-eight dogs (11.1%) developed PANS (Table 5) with the remaining 225 dogs (88.9%) not displaying any post-operative neurological complications. PANS score was mild (grade 1) in eleven dogs (39.3%), moderate (grade 2) in four dogs (14.3%) and severe (grade 3) in thirteen dogs (46.4%). Twelve dogs (42.9%) suffered post-operative generalized seizures (Table 4). Of the 28 dogs that suffered PANS, five (17.9%) did not survive to hospital discharge (Table 4). These dogs all suffered seizures meaning that 5/12 dogs (41.7%) that suffered seizures post-operatively died or were euthanized. None of the five dogs that died due to seizures received peri-operative levetiracetam, four out of the seven dogs that had seizures but survived to discharge did receive pre-operative leviteracetam.

Plasma osmolality was calculated at three time points. The median time interval from surgery to first sampling was 1 hour (range 0-4), from surgery to second sample was 8 hours (range 5-14) and from surgery to third sample was 24 hours (range 14-32). Osmolality was calculated at first sampling in 143 dogs with a median of 284.6 (269.6-316.0). Osmolality was calculated at second sampling in 131 dogs with a median of 282.7 (263.4-317.0). Osmolality was calculated at third sampling in 131 dogs with a median of 279.8 (265.5-325.4).

Univariable analysis

The results of the univariable binary logistic regression for possible risk factors of PANS and seizures are presented in Tables 5 and 6.

Multivariable analysis

The final model of risk factors for PANS included increasing age ($p<0.001$, Wald 16.561, odds ratio [Exp(B)] 1.476, confidence interval 1.223-1.780) and the presence of signs of HE immediately pre-operatively ($p=0.038$, Wald 4.305 odds ratio [Exp(B)] 2.704, confidence interval 1.057-6.922).

The final model of risk factors for seizures included increasing age ($p=0.009$, Wald 6.904, odds ratio [Exp(B)] 1.364, confidence interval 1.082-1.720) and the presence of signs of HE immediately pre-operatively ($p=0.048$, Wald 3.919 odds ratio [Exp(B)] 3.538, confidence interval 1.013-12.363).

Increasing age was significantly positively correlated with Osmolality 1 ($p<0.001$, $R=0.349$), Osmolality 2 ($p<0.001$, $R=0.387$), Osmolality 3 ($p<0.001$, $R=0.563$) and duration of clinical signs ($p<0.001$, $R=0.401$) and significantly negatively correlated with post-operative ammonia ($p=0.005$, $R=0.255$). Duration of clinical signs was significantly positively correlated with the duration of medical management ($p<0.001$, $R=0.311$).

Discussion

Although PANS do not occur frequently (11.1% in this study) they are a major cause of mortality in dogs that have undergone surgical CPSS attenuation. The unknown aetiology prevents aimed treatment and symptomatic treatment is centred on the use of anti-seizure medication to control neurological signs. Severe PANS may be refractory to such measures and this is reflected in a high mortality rate of 20-100%. [2,5–7,24,32,33]

PANS may develop due to the triggering of a change in the CNS environment following anaesthesia and surgery that has been "set up" by the prior exposure of the astrocytes to one or more substances implicated in the pathogenesis of HE.[6,9] To our knowledge there has not been identification of a risk factor that is predictive for PANS or seizure activity following surgical attenuation of a single CPSS. Our aim was to ascertain if clinical, biochemical or patient specific risk factors for PANS could be identified.

In this study the presence of HE immediately pre-operatively and age were independent risk factors for the development of PANS following surgical attenuation of a single CPSS. The odds of PANS occurring in dogs is increased 1.476 times with each year of age. The odds of PANS occurring in dogs with signs of HE immediately pre-surgery was 2.704 times that of those without.

Dogs that are older at the time of surgery have had longer exposure to alterations within the CNS. This fits with the suggestion that chronic and/or irreversible astrocyte damage by one or more neurotoxic substances is a trigger for the development of neurological

abnormalities when the dog is challenged by an anaesthetic and surgical procedure. This is consistent with previous findings suggesting that older dogs are at an increased risk of post-operative complications, neurological or otherwise.[2,6,7,9,23,34] A previous study suggested that age at diagnosis was not associated with long term survival and the authors concluded that there was no indication that surgical intervention should be performed early in life to be beneficial.[35] However, the results of the current study would suggest that delaying surgery could increase the risk of PANS.

Dogs that had signs of HE immediately prior to surgery either responded poorly to medical therapy or had not received medical therapy. CNS alterations may have been more severe, or the lack of medical therapy contributed to an unstable neurological state, resulting in a larger relative change in the CNS environment following shunt attenuation. The findings of the current study support the notion that alterations in the CNS pre-operatively are implicated in the neurological dysfunction seen post attenuation. This is in agreement with a previous study which indicated that dogs without pre-operative HE have fewer complications after CPSS attenuation, compared with dogs with pre-operative HE.[36] However, they are contrary to the results of another study which concluded that the presence of HE pre-operatively did not affect the likelihood of the development of PANS or seizure activity.[2] Other studies have not been able to draw any conclusions as to the significance of pre-operative HE in the development of PANS.[3,9] The reasons for discrepancies between studies are likely to include sample size, the retrospective nature of the studies and the lack of clarification of timing of observation of HE. The improvement of HE with medical management makes this information critical. The

281 separation of the clinical signs of pre-operative HE and post-operative PANS can be
282 difficult, particularly in dogs that have undergone partial shunt attenuation. In this study,
283 of the twenty eight dogs with PANS, nine dogs showed clinical signs of HE immediately
284 pre-operatively. Paired (pre and post-operative) ammonia samples in three of the dogs
285 affected by PANS showed a marked reduction in ammonia, lending evidence to two
286 distinct neurological syndromes, and not simply a continuation of HE.
287
288 Hyperammonaemia is a common finding in dogs with HE, yet dogs that have undergone
289 CPSS attenuation show a decrease in serum ammonia and this has been observed in dogs
290 with PANS.[13,24,33] The conversion of ammonia to glutamine within the astrocyte is
291 considered to be a factor in HE, resulting in osmotic stress and energy depletion.[16,37]
292 However the severity of neurological signs does not always correlate with
293 hyperammonaemia and serum levels of ammonia can be normal in dogs, cats and humans
294 with HE, suggesting other pathways are also involved. [13,38,39] Pre-operative ammonia
295 levels were not associated with the development of PANS in this study, suggesting that
296 the pathogenesis of PANS is complex and not related to a sole neurotoxin.
297
298 Interestingly, there were several risk factors evaluated in this study that were not found to
299 be predictive of PANS. Peri-operative treatment with levetiracetam was instigated at our
300 institution in 2012 as result of work by Fryer et al [3] suggesting peri-operative medication
301 with levetiracetam reduced the risk of developing seizures post-operatively. However in
302 the current study peri-operative levetiracetam did not affect the development of PANS or
303 seizure activity which is therefore inconsistent with the aforementioned paper that only

304 included dogs that developed seizures. Whilst prophylactic levetiracetam did not reduce
305 PANS or seizures in this study, it did seem to be associated with reduced mortality in
306 severely affected cases. However the cases receiving prophylactic levetiracetam were
307 recent and therefore reduced mortality could be explained by increased experience
308 treating PANS. It is also important to recognize that although cases receiving
309 levetiracetam were treated for at least 24 hours pre-operatively and five days post-
310 operatively, there may have been variation in the dose and duration of treatment. These
311 differences highlight the need for a prospective, controlled study to interrogate the role of
312 peri-operative anti-seizure medication for the prevention of PANS.
313
314 Neither extrahepatic or intrahepatic shunts were found to be at an increased risk of
315 developing PANS or seizure activity in this study. Previously, one study found that dogs
316 with extrahepatic shunts were significantly more likely to develop PANS and seizure
317 activity compared to intrahepatic shunts.[2] Additionally, the degree of attenuation
318 achieved was not predictive of neurological dysfunction in the current study.
319
320 In the univariable analysis age, the duration of the clinical signs, duration of medical
321 management and osmolality at time points 2 and 3 were all significant, but of these, only
322 age proved to be a risk factor in the multivariable model. The duration of clinical signs is
323 closely related to age and these were significantly correlated. There was also a significant
324 correlation between the duration of clinical signs and the duration of medical
325 management, which is not surprising. The presence of HE pre-operatively was not
326 significant in the univariable analysis but was a risk factor for PANS in the final model.

There were also significant correlations between osmolality and age. Osmolality, specifically sodium, has been implicated in the pathogenesis of HE in human medicine [16,29,40] and imbalance is likely to be implicated in HE in dogs, contributing to the alzheimer type II changes seen with astrocyte swelling. Interestingly, central pontine myelinolysis is associated with rapid correction of hyponatraemia,[28] and therefore increased osmolality. In the current study osmolality was greater in dogs affected by PANS and seizures. The significant differences in osmolality between dogs with and without PANS is an interesting finding and worthy of further study. It is possible that the changes in post-operative osmolality are directly related to the occurrence of PANS, it is also possible that they are result of PANS. Additionally, it is possible that osmolality is related to age.

The retrospective nature of this study is limiting, with smaller sub groups for several important variables, particularly osmolality. Although analysis of complications and behavioural changes used a detailed grading scale, retrospective analysis of these records is open to interpretation. Furthermore, information has been collected over an extended period. While this allows a large dataset to be analysed it also introduces variability in the surgical, anaesthetic and medical management.

Age and the presence of HE immediately pre-operatively were identified as risk factors for PANS and seizures in this study, suggesting surgery should not be delayed for a prolonged period and emphasizing the need to stabilise clinical signs of HE before

surgery. Further work is necessary to elucidate the underlying mechanism of PANS so that strategies can be targeted to prevent or more effectively treat PANS. Although it will be difficult to enroll sufficient dogs in a timely manner, a randomised, prospective study would be invaluable to confirm if there is any potential benefit of prophylactic anti-seizure medications in dogs undergoing surgery for a CPSS.

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Tables

Table 1*: Grading system for hepatic encephalopathy (HE) prior to medical therapy in dogs, adapted from Proot et al* [41]

HE Grade	Clinical signs
1	Normal, absence of abnormal clinical signs
2	Lethargy, apathy, minimal disorientation, subtle personality change, inappropriate behavior
3	Hypersalivation, severe ataxia, somnolence but responds to verbal stimuli, circling, head pressing
4	Coma, stupor, repeated seizures.

***Table 2**: Grading system for clinical response to pre-operative medical management of hepatic encephalopathy (HE) in dogs with a single congenital portosystemic shunt(CPSS)*[30]

Grade	**Clinical signs**
Good	No remaining clinical signs
Moderate	Some improvement but clinical signs of HE still present
Poor	Little or no clinical improvement

484 ***Table 3:*** *Grading system for Post Attenuation Neurological Signs (PANS) in dogs*
485 *undergoing surgical management of a single congenital portosystemic shunt (CPSS)*
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Grade	**Clinical signs**
1: Mild	Subtle depression or behavior change, mild tremors or twitching. Self resolves or responds immediately to anti-epileptic drug (AED) administration.
2: Moderate	Marked depression or behavior change, whole body tremors or twitching, +/- reduced response to visual stimuli. Requires one or more intravenous AED and ongoing increases in drugs with regular monitoring/ICU support to control PANS.
3: Severe	Progressive, severe depression/coma, nystagmus, complete blindness, seizures, requires maximum intervention with two or more AED +/- propofol and/or other drugs with continuous monitoring/ICU support.

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489 ***Table 4**: Details and outcome for 28 dogs affected by Post Attenuation Neurological*
490 *Signs (PANS) following surgical treatment of a single congenital portosystemic shunt*
491 *(CPSS)*
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Case	PANS grade	Nature of PANS	Pre op levetiracetam	Survival to discharge
1	1	Mild neurological signs for first few hours, resolved without treatment.	No	Yes
2	1	Inappropriate mentation 36 hours post surgery responded well to phenobarbitone and diazepam.	No	Yes
3	1	Prolonged recovery and ataxia, resolved with no treatment.	Yes	Yes
4	1	Mild tremor 36 hours post surgery quickly responsive to phenobarbitone.	No	Yes
5	1	Tremors and ataxia immediately post surgery, resolved with potassium bromide and levetiracetam.	No	Yes
6	1	Mild tremors 27 hours post surgery, resolved with no further treatment added to preoperative levetiracetam.	Yes	Yes
7	1	Mild tremors 96 hours post surgery, resolved with addition of phenobarbitone to preoperative levetiracetam.	Yes	Yes
8	1	Paddling forelimbs on recovery, resolved with midazolam.	No	Yes
9	1	Mild tremor resolved with no treatment.	No	Yes
10	1	Mild tremor 40 hours post surgery, resolved with addition of phenobarbitone to preoperative levetiracetam.	Yes	Yes
11	1	Tremors 24 hours post surgery, resolved with no treatment.	No	Yes
12	2	Depression, circling and ataxia, 48 hours post surgery resolved with phenobarbitone.	No	Yes
13	2	Depression, central blindness, head pressing 86 hours post surgery, gradual response to phenobarbitone.	No	Yes
14	2	Depression, visual and proprioceptive deficits 86 hours post surgery good response to phenobarbitone.	No	Yes
15	2	Depression, circling, central blindness 84 hours post surgery successful treatment with phenobarbitone.	No	Yes
16	3	Seizures12 hours post surgery, responded to phenobarbitone.	No	Yes
17	3	Seizures 12 hours post surgery good response to phenobarbitone, potassium bromide and diazepam.	No	Yes
18	3	Seizures at 72 hours post surgery. Successfully treated with phenobarbitone, levetiracetam and propofol CRI.	No	Yes
19	3	Seizures activity 6 hours post surgery, improved with phenobarbitone.	No	Yes
20	3	Circling, ataxia, visual deficits and seizure activity 78 hours post surgery resolved with addition of phenobarbitone to preoperative levetiracetam.	Yes	Yes

21	3	Seizures 28 hours post surgery, resolved with addition of phenobarbitone to preoperative levetiracetam.	Yes	Yes
22	3	Tremors, ataxia and seizures at 52 hours post surgery, resolved with the addition of phenobarbitone to preoperative levetiracetam.	Yes	Yes
23	3	Depression, ataxia and central blindness 90 hours post surgery, responded to phenobarbitone but still blind at discharge.	Yes	Yes
24	3	Seizures 24 hours post surgery, treated with phenobarbitone and propofol continuous rate infusion (CRI).	No	Euthanized
25	3	Seizures 48 hours post surgery, no response to phenobarbitone, propofol CRI controlled seizures but unable to wean off infusion.	No	Euthanized
26	3	Seizures 48 hours post surgery no response to phenobarbitone and diazepam. Propofol CRI controlled seizures but unable to wean off infusion.	No	Euthanized
27	3	Seizures 12 hours post surgery, refractory to phenobarbitone and propofol CRI.	No	Euthanized
28	3	Seizures 40 hours post surgery, refractory to phenobarbitone and levetiracetam. Responded to propofol CRI but developed aspiration pneumonia.	No	Euthanized

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Table 5: *Comparison of clinical variables for dogs with a single congenital portosystemic shunt (CPSS) that suffered post attenuation neurological signs (PANS) following surgical treatment and those that did not*

Variable	No PANS – 225 dogs	PANS – 28 dogs	P value
Type of shunt	Extrahepatic 173 (76.9%) Intrahepatic 52 (23.1%)	Extrahepatic 23 (82.1%) Intrahepatic 5 (17.9%)	0.532
Degree of attenuation	Complete 90 (40.0%) Partial 135 (60.0%)	Complete 15(53.6%) Partial 13 (46.4%)	0.173
Pre-operative albumin g/l	26.2 (7.9-35.5) 202 dogs	26.2 (22.0-35.8) 25 dogs	0.154
Pre-operative ammonia µmol/l	160 (range 8-544) 163 dogs	176 (range 36-590) 23 dogs	0.434
Post-operative ammonia µmol/l	86 (range 13-677) 105 dogs	56 (range 14-142) 14 dogs	0.061
Age in years	0.79 (0.20-7.80) 225 dogs	2.58 (range 0.33-11.98) 28 dogs	**<0.001**
Hepatic encephalopathy (HE) present prior to medical management	No 65 (28.9%) Yes 160 (71.1%)	No 6 (21.4%) Yes 22 (78.6%)	0.410
Duration of clinical signs pre-surgery in days	56 days (8-1436) 225 dogs	103 days (5-1269) 28 dogs	**0.020**
Duration of medical management pre-surgery in days	23 days (range 0-290) 225 dogs	21 days (range 0-730) 28 dogs	**0.037**
Response to medical management	Good 159 (75.4%) Moderate / poor 52 (24.6%)	Good 17 (63.0%) Moderate / poor 10 (37.0%)	0.172
Signs of HE immediately pre-operatively	No 186 (82.7%) Yes 39 (17.3%)	No 19 (67.9%) Yes 9 (32.1%)	0.065
Prophylactic anti-seizure medication	Yes 48 (21.3%) No 177 (78.7%)	Yes 6 (21.4%) No 22 (78.6%)	0.991
Osmolality at post-operative time point 1	284.5 (269.6-310.4) 129 dogs	286.0 (274.2-316.0) 14 dogs	0.067
Osmolality at post-operative time point 2	282.4 (263.4-310.4) 117 dogs	291.2 (269.1-317.0) 14 dogs	**0.016**
Osmolality at post-operative time point 3	279.8 (265.5-305.5) 121 dogs	285.2 (271.7-325.4) 10 dogs	**0.020**

Table 6: *Comparison of clinical variables for dogs with a single congenital portosystemic shunt(CPSS) that suffered seizures following surgical treatment and those that did not.*			
Variable	**No seizures – 241 dogs**	**Seizures – 12 dogs**	**P value**
Type of shunt	Extrahepatic 186 (77.2%) Intrahepatic 55 (22.8%)	Extrahepatic 10 (83.3%) Intrahepatic 2 (16.7%)	0.620
Degree of attenuation	Complete 98 (40.7%) Partial 143 (59.3%)	Complete 7 (58.3%) Partial 5 (41.7%)	0.234
Pre-operative albumin g/l	26.2 (range 7.9-35.8) 216 dogs	26.2 (range 23.0-31.5) 11 dogs	0.450
Pre-operative ammonia µmol/l	160.5 (range 8.0-562.0) 174 dogs	172.0 (range 36.0-590.0) 12 dogs	0.816
Post-operative ammonia µmol/l	85.0 (range 13.0-677.0) 113 dogs	52.7 (range 28.0-106.0) 6 dogs	0.156
Age in years	0.8 (range 0.2-12.0) 241 dogs	2.8 (range 0.8-8.5) 12 dogs	**0.006**
Hepatic encepalopathy (HE) present prior to medical management	No 68 (28.2%) Yes 173 (71.8%)	No 3 (25.0%) Yes 9 (75.0%)	0.809
Duration of clinical signs presurgery in days	55 days (range 5-1436) 241 dogs	195.5 days (range 54-385) 12 dogs	0.162
Duration of medical management pre-surgery in days	24 days (range 4-730) 226 dogs	25 days (range 6-181) 12 dogs	0.689
Response to medical management	Good 169 (74.8%) Moderate / poor 57 (25.2%)	Good 7 (58.3%) Moderate / poor 5 (41.7%)	0.215
Signs of HE immediately pre-operatively	No 198 (82.2%) Yes 43 (17.8%)	No 7 (58.3%) Yes 5 (41.7%)	0.051
Prophylactic anti-seizure medication	Yes 51 (21.2%) No 190 (78.9%)	Yes 3 (25.0%) No 9 (75.0%)	0.752
Osmolality at post-operative time point 1	284.5 (range 269.6-310.4) 138 dogs	295.1 (283.4-316.0) 5 dogs	**0.001**
Osmolality at post-operative time point 2	282.3 (range 263.4-310.4) 126 dogs	298.0 (range 294.1-317.0) 5 dogs	**0.002**
Osmolality at post-operative time point 3	279.8 (range 265.5-305.5) 127 dogs	293.7 (range 285.1-325.4) 4 dogs	**0.006**

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