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REVIEW

Postattenuation neurologic signs after surgical attenuation of congenital portosystemic shunts in dogs: A review

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Abstract
The development of postattenuation neurologic signs (PANS) is a poorly understood and potentially devastating complication after surgical attenuation of congenital portosystemic shunts in dogs. Postattenuation neurologic signs include seizures but also more subtle neurologic signs such as depression, after the first two authors, the author list is alphabetical.

This manuscript represents a portion of a thesis submitted by Dr Mullins to University College Dublin as partial fulfillment of the requirements for a Doctorate of Veterinary Medical Specialization.

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behavioral changes, tremors, and twitching. They most commonly occur within 7 days postoperatively and are typically unrelated to hyperammonemia, hypoglycemia, or electrolyte disturbances. This narrative review summarizes the findings of 50 publications from 1988-2020 that report occurrence of PANS. While most published reports included only dogs affected by postattenuation seizures (PAS), others included dogs with any form of PANS. Overall, PANS (including PAS) affected 1.6%-27.3% of dogs, whereas incidence of PAS ranged from 0%-18.2%. The etiology of PANS remains unknown; however, several theories have been proposed. Risk factors include preoperative hepatic encephalopathy, increasing age, and possibly certain breeds and extrahepatic shunt morphology. There is increasing evidence that prophylactic antiepileptic drugs do not prevent PANS. Treatment is centered around controlling neurologic signs with antiepileptic drugs and providing supportive intensive care. The 30-day survival rate in studies that included a minimum of four dogs affected by PANS was 0%-100% (median, 50.0%) and 0%-75.0% (median, 37.5%) for those with PAS. Mortality associated with PANS was typically related to occurrence of generalized seizure activity. Prognostic factors positively associated with short-term survival included having a history of preoperative seizures and development of focal seizures only. If affected dogs survived to discharge, survival for several years was possible, and the majority of neurologic signs manifested as part of the phenomenon of PANS appeared to resolve.

1 | INTRODUCTION

In 1988, Mathews and Gofton reported fatal postattenuation seizures (PAS) in 3 dogs without preoperative seizures after surgical attenuation of a congenital extrahepatic portosystemic shunt (cEHPSS). Since then, occurrence of PAS or other postattenuation neurologic signs (PANS) has been mentioned or described in detail in 49 further reports. Several terms have been used to describe this complication, including postligation seizure syndrome, postligation neurologic dysfunction, postligation neurologic syndrome, postligation seizures, posttattenuation neurologic signs, and posttattenuation seizures. While several investigators have described the occurrence of seizures, others have recognized that this phenomenon can manifest as more subtle neurologic signs such as depression, ataxia, behavioral change, tremors and twitching. Posttattenuation neurologic signs has been defined as manifestation of any postoperative neurologic signs (including seizures) between surgery and discharge (most commonly within 7 days postoperatively) and typically unrelated to hyperammonemia, hypoglycemia, or electrolyte disturbances. This complication is considered distinct to hepatic encephalopathy (HE) for several reasons, including its occurrence even after complete shunt ligation and in dogs without preoperative neurologic signs or seizures, its frequently refractory nature in comparison to preoperative neurologic signs, and its occurrence even in the face of normal or near normal ammonia concentrations.

The objective of this narrative review is to summarize the available literature pertaining to incidence, etiology, and risk factors for PANS in dogs, as well as the use of prophylactic antiepileptic drug(s) (AEDs), treatment, and prognosis for survival and outcome.

2 | SEARCH STRATEGY

An electronic literature search was performed in January 2021 using the PubMed database (www.ncbi.nlm.nih.gov/PubMed) with the aim of identifying all peer-reviewed articles without date restriction that reported occurrence of PANS in dogs. Search strategy details are presented in Appendix S1 in File S1. Exclusion criteria included articles in a non-English language, experimental or in vitro studies, reviews, editorials, letters to the editor, and studies that did not describe occurrence of PANS. Potential additional references were searched from reference lists of final PubMed selected articles. Article selection and data extraction were performed by the primary author. The electronic search identified 962 citations, of which 706 were excluded based on their title and abstract. The
remaining 256 manuscripts were read in full, with 48 articles meeting the inclusion criteria.\textsuperscript{2,4–30} Reference lists within these 48 articles were hand searched for potential additional references, which yielded a further two articles meeting the inclusion criteria.\textsuperscript{1,3} Reference lists within these two articles were again hand searched and no further articles were identified.

3 | INCIDENCE OF POSTATTENUATION NEUROLOGIC SIGNS

Most published reports include only dogs affected by PAS,\textsuperscript{1,2,4–6,9,12,16,17,23–27,29–35,37–40,42,45–49} but others include dogs that manifest any form of PANS.\textsuperscript{5,10,11,13–15,18–22,28,36,41,43,44,50} Within the latter reports,\textsuperscript{5,10,11,13–15,18–22,28,36,41,43,44,50} PANS affected 2.6%-27.3% of dogs. Overall, PANS (including PAS) affected 1.6%-27.3% of dogs (Appendix S2 in File S1).\textsuperscript{1,2,4–11,13–15,18–29,31–37,39–46,48–50} The true incidence of PANS may be underreported as subtle neurologic signs may go unrecognized.\textsuperscript{36,41} Postattenuation seizures are described predominantly after attenuation of eEHPS, with a reported incidence of 0%-18.2%.\textsuperscript{1,2,4–7,10,11,13,15,18,19,23,25–27,29,31,32,34,37,39,44–46,48–50} Incidence of PAS after congenital intrahepatic portosystemic shunt (cHPSS) attenuation ranges from 0%-14.3% (Appendix S2 in File S1).\textsuperscript{7,9,19,22,26,40,41,43}

4 | ETIOLOGY OF POSTATTENUATION NEUROLOGIC SIGNS

Etiology of PANS remains unknown; however, several theories have been proposed.

4.1 | Central nervous system (CNS) disease/derangement

4.1.1 | Altered central nervous system metabolism

Based on a single study,\textsuperscript{51} one PANS theory is that a decrease in systemic concentrations of endogenous benzodiazepines derived from the gastrointestinal tract occurs after shunt attenuation. Mean concentrations of endogenous benzodiazepines in portal and arterial blood of 15 dogs with congenital portosystemic shunts (cPSS) were significantly (\(P < .05\)) higher than those of eight healthy controls.\textsuperscript{51} Investigators proposed that if shunting caused stimulation of brain benzodiazepine receptors, a decline in systemic concentrations after shunt attenuation could result in seizures.\textsuperscript{51} A decrease in cerebrospinal fluid (CSF) concentrations of endogenous benzodiazepines and changes in concentrations of neurotransmitters have also been theorized to precipitate seizures.\textsuperscript{2} This theory relating to a decline in systemic or CSF endogenous benzodiazepine concentrations fails to explain the occurrence of PANS after partial ligation,\textsuperscript{1,2,4,9,13,15,16,18,19,43,46} and delayed attenuation techniques.\textsuperscript{10,13,17–19,21,23,25–28,30,32,34,37,39,40,44–50} Administration of benzodiazepines has also proven unreliable in the management of PANS.\textsuperscript{2,13,17,18,32}

It is recognized that dogs with cPSS have significantly (\(P < .0001\)) increased whole blood manganese concentrations compared with healthy controls.\textsuperscript{52} In rats, exposure of astrocytes to manganese is associated with upregulation of “peripheral type” benzodiazepine receptors;\textsuperscript{53} however, an association in dogs has not been investigated. Torisu and colleagues\textsuperscript{54} identified hyperintensity of the lentiform nuclei on T1-weighted images in dogs with cPSS, which decreased after surgical attenuation. In a case report by the same investigators,\textsuperscript{30} lentiform nuclei were confirmed to have significantly higher (> 4 times) manganese concentrations (as well as approximately twice the concentration of iron and copper) in a dog with PAS that was euthanized compared with a control group.

Postattenuation neurologic signs do not appear to be a manifestation of postoperative hyperammonemic-HE and seem distinct from neurologic signs observed preoperatively related to HE.\textsuperscript{16} They are reported predominantly in the presence of normal/near normal or significantly decreased (compared with preoperatively) ammonia concentrations,\textsuperscript{1,4,12,13,16,32,38,41,46} with only a few reported cases with concurrent hyperammonemia.\textsuperscript{2,4,30,41,46} In a retrospective study involving 253 dogs (28 of which developed PANS),\textsuperscript{41} no significant difference in preoperative or postoperative ammonia concentrations was identified among dogs that did or did not experience PANS or PAS. In another retrospective study involving 75 dogs affected by PAS,\textsuperscript{46} ammonia concentrations around the time of PAS occurrence were <70.0 \(\mu\)mol/L in 76.7% of dogs for which values were available. In a further retrospective study involving 93 dogs with PAS (many of which were included in the previous study\textsuperscript{46}),\textsuperscript{47} dogs with a history of preoperative seizures had a median ammonia concentration of 46.0 (range, 13.0-104.0) \(\mu\)mol/L (<70 \(\mu\)mol/L considered normal)\textsuperscript{41,47} at the time of PAS. Some dogs with HE can have normal ammonia concentrations and the possibility of an unknown biochemical factor resulting in a nonhyperammonemic HE has been proposed as an explanation for PANS.\textsuperscript{4,55} However, absence of preoperative HE in some dogs and the refractory nature of PANS in comparison to preoperative HE suggest an alternative etiology than postoperative continuation of HE.\textsuperscript{4,17} Investigators in an older retrospective
case series\textsuperscript{2} considered the presence of HE-induced brain lesions as a possible cause for \textit{PAS} in four dogs; however, histologic signs supporting this were not identified on necropsy of two brain specimens.\textsuperscript{2}

Occurrence of one or more postoperative metabolic events in the face of shunting-induced CNS damage has been theorized to result in \textit{PAS}.\textsuperscript{2} It has also been suggested the CNS of dogs with cPSS becomes adapted to a state of altered metabolism and that a change in this altered metabolic state postattenuation precipitates \textit{PAS}.\textsuperscript{4,13} The presence of HE immediately preoperatively has been identified as a risk factor for \textit{PANS} and \textit{PAS},\textsuperscript{41} with investigators proposing that a larger relative change in CNS environment postattenuation could be responsible for \textit{PANS}.\textsuperscript{41}

4.1.2 | Concurrent brain disease

Concurrent brain disease, including idiopathic epilepsy, congenital, inflammatory and noninflammatory brain disease, has been suggested as a possible cause of \textit{PANS}.\textsuperscript{2,13,44} A congenital etiology, cerebral cortical disease, and idiopathic epilepsy were considered unlikely by investigators in a small retrospective case series\textsuperscript{2} because of the positive preoperative response to treatment of HE in three affected dogs and absence of preoperative neurologic signs in another dog. In another retrospective case series,\textsuperscript{4} only 2 of 5 dogs with generalized \textit{PAS} demonstrated preoperative neurologic signs, suggesting that pre-existing brain disease was not responsible for postoperative generalized seizures. A limitation of these case series\textsuperscript{2,4} is that they include a total of only 9 dogs. Evidence of inflammatory or congenital (eg, hydrocephalus) brain disease has not been identified on necropsy in affected dogs.\textsuperscript{2,4,20,23,39,44} Cerebrospinal fluid obtained from three dogs with cPSS identified mild inflammation in two\textsuperscript{2,4} (suspected due to prolonged seizure activity in one dog),\textsuperscript{2} and was normal in the third dog.\textsuperscript{1} In a retrospective study,\textsuperscript{44} no evidence of necrotizing meningoencephalitis was identified on necropsy in any pug that developed \textit{PANS} and subsequently died. Reyev's syndrome, a rare and potentially fatal illness in people involving acute noninflammatory encephalopathy with fatty liver failure, has also been suggested as a possible cause of \textit{PAS} but it was considered unlikely on the basis of decreased ammonia concentrations postoperatively and lack of elevated liver enzymes.\textsuperscript{2} As far as we are aware, Reyev's syndrome has not been reported in dogs. Using single photon emission computed tomography (SPECT), one study demonstrated areas of regional hypoperfusion and hyperperfusion within the brain of 8 dogs with cPSS and HE compared with 8 normal dogs.\textsuperscript{56}

4.1.3 | Acquired brain disease

Hypertensive encephalopathy has been considered a possible cause of \textit{PAS}.\textsuperscript{2} However, blood pressure during seizure activity has been reported in only four dogs and was within normal limits in all cases.\textsuperscript{5,32} Severe intraoperative hypotension has also been suggested as a cause of \textit{PAS} because of secondary brain ischemia and subsequent neuronal necrosis.\textsuperscript{39} However, no difference in incidence of \textit{PAS} among dogs that did (8.4\%) or did not (7.4\%) experience intraoperative hypotension was identified in one retrospective study.\textsuperscript{39} Finally, hypoxemia/brain hypoxia has been proposed as a possible cause of \textit{PAS};\textsuperscript{2,4,32,44} however, there is no strong evidence to support this. In two small retrospective case series,\textsuperscript{2,4} lesions consistent with hypoxia/anoxia identified in brain specimens of four nonsurvivors were suspected to be due to seizure activity rather than a cause.

4.2 | Perioperative hypoglycemia

Perioperative hypoglycemia is a recognized complication of eHPSS attenuation in small dogs.\textsuperscript{57} Hypoglycemia is sporadically reported in dogs with \textit{PAS}\textsuperscript{1,2,4,46,47} but there are many reported cases of \textit{PANS} and \textit{PAS} that occurred with normoglycemia.\textsuperscript{1,4,10,13,16,17,32,38,39,44,46} In a retrospective study involving 75 dogs with \textit{PAS},\textsuperscript{46} glucose concentrations at the time of seizure occurrence were ≥3.3 mmol/L in 91.9\% dogs for which values were available. There are at least four reports of affected dogs receiving dextrose-containing fluids or eating voluntarily when \textit{PANS} first commenced.\textsuperscript{1,4,12,13} Postattenuation neurologic signs can also progress despite treatment to correct hypoglycemia.\textsuperscript{2,4} Hypoglycemia-induced brain lesions may be an explanation but this concept has not been investigated.\textsuperscript{2}

4.3 | Perioperative electrolyte disturbances

Variable degrees of derangement in electrolyte concentrations have been identified in a limited number of dogs at the time of \textit{PAS}.\textsuperscript{2,4,16,25,47} Low to low-normal total calcium concentrations have been reported in at least seven dogs affected by \textit{PAS}; however, ionized hypocalcemia was confirmed in only a single dog.\textsuperscript{2,13,16} Intravenous calcium supplementation in at least two of these dogs did not arrest seizures.\textsuperscript{2,13} Hypokalemia has also been identified in dogs affected by \textit{PAS} and correction similarly did not always abolish seizures.\textsuperscript{2,16,46,47} There are many more reported cases of \textit{PAS} occurring in the face of normal
electrolyte concentrations and the potential contribution of electrolyte derangement to occurrence of PANS remains unclear.12,32,38,46,47

4.4 | Postoperative portal hypertension

A clear association between PANS and portal hypertension has not been demonstrated and there are several reports of PANS despite intraoperative measurement of portal pressures and adherence to recommended guidelines for attenuation.1,2,4,10–12,17,41 There are occasional reports of portal pressures measured at the time of PAS.2,4 In one affected dog, portal pressures measured via a catheter that had been left in situ in a jejunal vein were consistently within normal limits.4 No evidence of portal hypertension was identified, either grossly or following measurement of portal pressures in two affected dogs that underwent repeat celiotomy during PAS.2,4 There is one report11 of PANS persisting after ligature removal for treatment of concurrent postoperative portal hypertension and another report10 of PANS developing after ligature removal. No gross evidence of portal hypertension was identified at necropsy in two dogs.5

4.5 | Infectious disease

An infectious cause for PANS has not been identified. In a small case series,2 serologic testing for canine distemper virus in two dogs yielded negative results and CSF bacterial culture from one dog failed to identify a causative organism.

5 | Risk factors for postattenuation neurologic signs

Potential risk factors for PANS include:

5.1 | Presence of immediately preoperative hepatic encephalopathy

Neurologic signs consistent with HE are frequently diagnosed in dogs with cPSS but few studies report the prevalence of HE immediately preoperatively.41 In a retrospective study involving 253 dogs,41 the presence of HE immediately preoperatively was a risk factor for PANS (odds ratio [OR] 2.704, CI 1.057-6.922) and PAS (OR 3.538, CI 1.013-12.363). The presence of more severe CNS changes8,59 (eg, astrocyte swelling caused by neurotoxic substances such as ammonia), a less stable neurologic state, and a greater relative change in CNS biochemical environment after shunt attenuation were considered to be implicated.41 This highlights that preoperative medical stabilization of HE should be a priority where possible.

5.2 | Increasing age

Increasing age has been identified in a recent study as a risk factor for PANS (OR 1.476, CI 1.223-1.780) and PAS (OR 1.364, CI 1.082-1.720).41 corroborating observations of several previous investigators.2,4,13,23,41,44,46,47 It has been suggested that the brain of older dogs is exposed to the abnormal metabolic consequences of shunting for longer or becomes adapted to a state of abnormal metabolism, with shunt attenuation in such dogs precipitating PANS.4,41 Postattenuation neurological signs have also been reported in dogs <12 months old1,2,4,16,17,21,23,25,32,41,43,47 and some studies report no significant difference in age of dogs that did or did not develop PANS.13,21,44

5.3 | Extrahepatic portosystemic shunt morphology

Postattenuation neurological signs (including PAS) have been reported predominantly after correction of cEHPSS,1,2,4,10—13,15,18,19,21,23,25,27—29,31,32,34,37—39,41,44—50 with fewer reports after cHPSS attenuation.5,7,9,16,17,21,22,26,36,40,41,43 In one retrospective study involving 89 dogs, 13 those with cEHPSS (12.4%) were more likely (P = .03) to develop PANS than dogs with cHPSS (0.0%). However, this is not supported by two larger retrospective studies involving 106 and 253 dogs, respectively.21,41 The incidence of PAS after cEHPSS attenuation is 0%–18.2%1,2,4,7,10,11,13,15,18,19,21,23,25,27—29,31,32,34,37,39,41,44—46,48–50 and 0%–14.3%7,9,19,22,26,40,41,43 after cHPSS attenuation (Appendix S2 in File S1). PANS are reported after attenuation of portocaval, portophrenic, and portoazygos shunt submorphologies.10,13,46,47 One retrospective study identified a trend toward dogs with portoazygos shunts being at greater risk of PANS than dogs with portocaval shunts.13 Dogs with portoazygos shunts tend to be older at diagnosis than dogs with portocaval shunts and it is possible that their older age is responsible for increased risk of PANS in such dogs rather than the shunt submorphology.13

5.4 | Certain breads

Certain breeds have been suggested to be at increased risk of PANS, including Jack Russell terriers,21 pugs10,13,44 and Maltese1,13 However, these observations are derived from small study populations.
6 | FACTORS THAT HAVE NOT BEEN FOUND TO BE ASSOCIATED WITH INCREASED RISK OF POSTATTENUATION NEUROLOGIC SIGNS

6.1 | Method and degree of acute intraoperative shunt attenuation

Postattenuation neurologic signs are reported after complete and partial suture ligation, delayed attenuation techniques, including thin film banding (TFB), aminon constrictor (AC) placement, and endovascular techniques. The incidence of PANS after suture ligation, TFB and AC placement is 0%-18.2%, and no significant difference in incidence of PANS among dogs with cIHPSS treated with TFB or AC. No significant difference in incidence of PANS was identified among dogs with cIHPSS that underwent partial attenuation with silk (14.3%) or TFB (11.4%) in another study. Case and colleagues reported PANS in 9.7% dogs with cIHPSS after TFB and 3.7% after coil embolization; however, the investigators did not state if the difference was statistically significant.

No association has been identified between degree of acute intraoperative shunt attenuation and occurrence of PANS. In one retrospective study, 8.3% of dogs undergoing complete ligation with silk experienced PANS, in comparison to 13.0% of dogs that underwent partial attenuation with silk or TFB (P = .6). In a large-scale retrospective study, the degree of shunt attenuation (complete ligation vs. TFB or partial ligation) was not associated with PANS or PAs. Degree of intraoperative shunt occlusion with TFB (<3 mm versus no occlusion) was also not associated with occurrence of PANS in another study.

6.2 | Preoperative neurologic signs or seizures

As discussed previously, the presence of immediately preoperative hepatic encephalopathy has been identified as a risk factor for PANS and PAS. However, a clear association between presence of preoperative neurologic signs or seizures overall (not just in the immediate preoperative period) and occurrence of PANS or PAS has not been identified. In three large retrospective studies, no difference in the incidence of PANS or PAS was identified among dogs that did or did not have preoperative neurologic signs/HE. However, investigators in two of these studies do not report specific timing of neurologic signs prior to surgery. Absence of preoperative neurologic signs/HE (prior to medical management or immediately preoperatively) does not exclude the possibility of PANS. In a study that included 93 dogs affected by PAS, approximately 25% of affected dogs did not have preoperative neurologic signs and only 17.2% had preoperative seizures. In another retrospective study, only 1 of 7 dogs with PAS had preoperative seizures, while in 3 small case series and a case report, no dog with generalized PAS had a history of preoperative seizures.

6.3 | Surgical or anesthesia time

In a retrospective study that included 124 dogs, neither surgical nor anesthetic time was significantly different among dogs that did or did not experience PAS.

6.4 | Postoperative changes in natremia/serum osmolality

Investigators in a retrospective study proposed that PANS may be related to postoperative changes in natremia/osmolality. In that study, serum osmolality was significantly higher at two postoperative time points (median of 8 [P = .016] and 24 h [P = .020] postoperatively) in dogs affected by PAS and at all 3 postoperative time points (median of 1 [P = .001], 8 [P = .002], and 24 h [P = .006] postoperatively) in dogs affected by PAS compared with unaffected dogs. However, osmolality did not remain statistically significant in the multivariable analysis. There are no further studies investigating serum osmolality in dogs with PAS.

7 | USE OF PROPHYLACTIC ANTIEPILEPTIC DRUGS (AEDs)

Efforts to reduce the incidence of PANS have included prophylactic treatment with AEDs including benzodiazepines, phenobarbital, potassium bromide, and levetiracetam. None of these has unequivocally been demonstrated to reduce the incidence of PANS in dogs with cPSS; however, without
measurement of plasma drug concentrations, any conclusions regarding the efficacy of these AEDs is tentative.

7.1 | Levetiracetam

There are conflicting reports regarding the possible protective effect of prophylactic treatment with levetiracetam against development of PAS. In one retrospective study, none of 42 dogs that had received preoperative levetiracetam, 20 mg/kg every 8 h (q8) for at least 24 h, experienced PAS, whereas four (4.8%) of 84 dogs that had not received levetiracetam developed PAS. This observation, however, was not supported by four subsequent larger retrospective studies. In one retrospective study, 6 (11.1%) of 54 dogs that had received prophylactic levetiracetam (20 mg/kg q8 for ≥24 h preoperatively and for ≥5 days postoperatively) developed PAS, whereas 22 (11.1%) of 199 dogs that had not received levetiracetam experienced PAS. Investigators also found a similar incidence of PAS among dogs that had or had not received levetiracetam (5.6% and 4.5%, respectively). In another large retrospective study, the incidence of PAS was not significantly different among dogs that did (11.2%) or did not (6.7%) receive levetiracetam at ≥15 mg/kg q8 for ≥24 h preoperatively or a 60 mg/kg intravenous loading dose perioperatively, both followed by ≥15 mg/kg q8 postoperatively. However, the same levetiracetam protocol was not followed in all cases in that study. A limitation of all published studies describing prophylactic treatment with levetiracetam is their retrospective nature and lack of randomization and standardization of treatment. Some studies provide no information regarding preoperative or postoperative dose or duration of levetiracetam. In the study by Fryer and colleagues, some dogs did not receive any postoperative levetiracetam, with the authors placing emphasis on pretreatment. According to a pharmacokinetic study, failure to continue levetiracetam postoperatively, and at the appropriate dosage (20 mg/kg q8), would be expected to result in plasma drug concentrations decreasing below the recommended therapeutic range (5-45 μg/ml) after approximately 12 h. In another study, some dogs prescribed levetiracetam received concurrent phenobarbital and/or potassium bromide, a practice that has been shown to alter the pharmacokinetics of levetiracetam significantly. Wallace and colleagues described the administration of levetiracetam for a median (range) of 23 (1-29) days preoperatively and four (2-4) weeks postoperatively in six dogs that underwent cEHPSS attenuation with a polycrylic acid-silicone device, none of which experienced PAS, but that study did not include a control group.

7.2 | Phenobarbital

Prophylactic treatment with phenobarbital has not been demonstrated to reduce the incidence of PAS but one retrospective study suggested that it may reduce its severity. In that study, prophylactic phenobarbital (5-10 mg/kg before induction followed by 3-5 mg/kg q12 for 3 weeks postoperatively) did not significantly decrease the incidence of PAS (6.5%) compared with a control population (15.5%). However, no dog that received phenobarbital experienced generalized PAS. Inadequacy of presurgical loading was suggested as a reason for failure to prevent PAS in that study completely, although serum phenobarbital concentration at the time of PAS occurrence was within therapeutic range in the one dog in which it was measured. In a retrospective study involving 106 dogs, PAS were observed in 9.4% dogs despite most having received perioperative phenobarbital (5-10 mg/kg) and for 2 weeks postoperatively (2-5 mg/kg q12).

7.3 | Potassium bromide

Few studies report prophylactic treatment with potassium bromide and a protective effect has not been identified. In a retrospective study involving 28 dogs with cEHPPS, one dog that had received a 24-h preoperative loading regimen of potassium bromide (100 mg/kg q6) experienced PAS. However, no information is provided regarding the overall number of dogs that received prophylactic potassium bromide. In another retrospective study involving 168 dogs with cEHPPS, four (8.3%) of 48 dogs that had received preoperative treatment with potassium bromide (44-100 mg/kg q24 for at least two weeks preoperatively) developed PAS compared with four (3.3%) of 120 dogs that did not receive potassium bromide. No information is provided regarding whether treatment was continued postoperatively in affected dogs.

8 | Treatment of Postattenuation Neurologic Signs

The idiopathic nature of PAS precludes accurate treatment of a specific cause. Treatment is therefore centered around providing supportive care measures and controlling neurologic signs using AEDs, including benzodiazepines, barbiturates, propofol, alfaxalone, potassium bromide, α-2 agonists, and benzodiazepine.
antagonists. There are no prospective randomized studies evaluating efficacy of one or more AEDs/treatment protocols. In a retrospective study involving 93 dogs affected by PAS, no drug was associated with improved short-term survival in the multivariable analysis. A limitation of current literature is that treatment is nonrandomized and based on clinician preference. Because multiple AEDs are often administered concurrently and more aggressive treatments are likely to have been administered to more severely affected cases, interpretation of results is difficult.

In some cases, mild neurologic signs resolve without treatment, whereas other cases progress to refractory seizures, highlighting that very close monitoring is required. Treatment of PAS with benzodiazepines is controversial. As discussed previously, one older study suggested a decline in systemic concentrations of endogenous benzodiazepines after shunt attenuation could precipitate PAS. This would suggest that prophylactic treatment with benzodiazepines may be efficacious in the prevention or treatment of PAS. However, in the majority of studies in which an assessment of the response to treatment of PAS with benzodiazepines is possible, they failed to control neurologic signs, particularly in cases of generalized PAS. There are several reports of treatment of PAS with propofol CRI, typically resulting in rapid control of even refractory seizures. Anecdotally, it has been suggested that use of propofol for management of PAS may be associated with elimination of external manifestations of seizure activity but may not arrest the brain activity causing the seizures. To our knowledge, this has not been investigated in dogs. Prior to the first reports of using propofol for control of PAS, barbiturates including pentobarbital and thiopental were administered in cases refractory to benzodiazepines. There are several reports of treatment of PAS and specifically PAS with phenobarbital, with mixed but mostly positive results.

While levetiracetam is relatively frequently described as a prophylactic AED in recent literature, there are few reports describing its efficacy in the treatment of PAS. In one retrospective study, 9 dogs with PAS received treatment with levetiracetam, including 5 dogs with PAS. However, in 8 of those 9 dogs, other AEDs including phenobarbital and propofol were administered concurrently with levetiracetam, and in 1 case, PAS were described as refractory to levetiracetam. Treatment of PAS with levetiracetam was also not significantly associated with short-term survival in a more recent study.

The 30-day survival rate in studies of ≥4 dogs affected by PAS overall is 0%-100% (median, 50.0%) and for PAS specifically (n ≥ 4 dogs) is 0%-75.0% (median, 37.5%) (Appendix S3 in File S1). Such variation in survival rates is likely related to varying numbers of dogs within reports and those with generalized versus focal PAS or more subtle PANS, different levels of experience in treating PAS and the extent to which they are treated, and possibly the managing clinician’s perception of prognosis. Dogs that experience PAS other than PAS and those that experience focal PAS only (in comparison to generalized PAS) have a better outlook for survival. In a large retrospective study, all dogs with PAS other than seizures survived to discharge compared with the 58.3% of 12 dogs that experienced PAS. In another retrospective study, dogs that experienced seizures or coma did not respond to treatment, whereas all those with more mild PAS survived. However, knowing that mild PAS are associated with a better prognosis has limited prognostic value as it is impossible to predict whether more subtle neurologic signs will progress to seizures. Among 76 dogs with generalized PAS in one study, 13 (17.1%) were recorded as having experienced focal PAS that later progressed to generalized PAS. Generalized PAS may be more refractory to treatment, more distressing for the owner to observe, associated with a greater financial cost and the perception of a poorer prognosis for recovery, all of which may influence the decision to euthanize. In a retrospective study involving 7 dogs with PAS, all dogs with focal PAS only survived to discharge, whereas none of those with generalized PAS survived. In another retrospective study involving 93 dogs with PAS, only 32.3% dogs survived to 30 days; however, the majority experienced generalized PAS, which were significantly associated with mortality. In that study, 21.1% of dogs with generalized PAS survived to 30 days in comparison to 82.4% of dogs with focal PAS only (P = .0003). Dogs with PAS that had a history of preoperative seizures had significantly increased odds of survival to 30 days compared with those that did not have preoperative seizures. This corroborates findings of an earlier retrospective study in which dogs with a history of preoperative seizures that subsequently experienced PAS had a sevenfold increased probability of survival (to discharge) compared with those without a history of preoperative seizures. It is possible that PAS experienced by both subsets of dogs may have a different etiopathogenesis or some dogs with
preoperative seizures (related to HE) may have continuation of these seizures postoperatively.39,46,47 There are no large-scale studies investigating neurologic outcomes of dogs affected by PANS that survive to 30 days but several reports document reoccurrence of seizure activity in the long term (>30 days).2,4,10,12,13,16,38 Without follow-up assessment of shunt closure, it is possible that return of neurologic signs or seizures could be related to the reoccurrence or persistence of HE because of residual or acquired shunting. If affected dogs survive to discharge, survival for several years is possible.3,32,38 On the basis of the overall small number of published reports, and specifically those describing long-term outcomes, and inconsistent follow-up times within reports, it is difficult to provide meaningful prognostic information regarding survival time and neurologic outcomes to owners of affected dogs.2,4,10,12,13,16,38 The majority of neurologic signs manifested as part of PANS appear to resolve.2,4,10,12,13,16,38 However, exact timing of resolution of signs is difficult to determine due to inconsistent follow up and lack of standardization of follow-up times. There are also no published studies investigating the long-term quality of life of dogs affected by PANS.

10 | CONCLUSION

The development of PANS is a potentially devastating complication after cPSS attenuation in dogs. Overall, PANS (including PAS) affect 1.6%-27.3% of dogs. Post-attenuation seizures are described predominantly after attenuation of cEHSS, with a reported incidence of 0%-18.2%; however, this may reflect the greater frequency of cEHSS in dogs compared with cIHPSS. The etiology of PANS remains elusive; however, a number of risk factors have been identified, including increasing age and presence of HE immediately preoperatively. A history of preoperative seizures is associated with improved survival for dogs that develop PAS. Certain breeds may also be predisposed to PANS. There is increasing evidence to suggest that prophylactic treatment with levetiracetam does not prevent PANS. Treatment of PAS is supportive and centered around administration of AEDs as the idiopathic nature of PANS precludes specific treatment. Generalized PAS can be particularly refractory to treatment and the prognosis for dogs affected by such is generally poor. Dogs with less severe PANS are more likely to survive but progression to more severe signs has been reported. Overall, if affected dogs survive to discharge, survival for several years is possible, and the majority of neurologic signs manifested as part of PANS appear to resolve.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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REFERENCES


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