Royal
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1 **Health Related Quality of Life following Surgical Attenuation of Congenital**

2 **Portosystemic Shunts versus Healthy Controls**

3

4 **Summary**

5 **Objectives:** To design a health-related quality of life questionnaire for dogs with

6 congenital portosystemic shunts, use this in a cohort of dogs treated with suture

7 attenuation and compare results with that from a healthy control cohort.

8 **Methods:** Data were collected from the hospital records of dogs treated with suture

9 ligation of an intrahepatic or extrahepatic congenital portosystemic shunt at two referral

10 centres. Owners were asked to complete a questionnaire assessing their dog's health-

11 related quality of life pre-operatively (retrospectively) and at the time of follow-up.

12 Owners of control dogs also completed the questionnaire.

13 **Results:** 128 dogs with congenital portosystemic shunts and 131 control dogs were

14 recruited. Median follow-up time was 64 months (range 19.7-157.2). The median long-

15 term health-related quality of life score was excellent for both intrahepatic (94/100) and

16 extrahepatic (96/100) shunt cases and similar to that of control dogs. The long-term

17 median CPSS scores of both IHCPSS and EHCPSS dogs were significantly worse than the

18 control group.

19 **Clinical significance:** Suture attenuation of congenitial portosystemic shunts is

20 associated with an excellent health-realted quality of life score at long-term follow-up.

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Introduction

A congenital portosystemic shunt (CPSS) is an abnormal vascular communication that diverts blood away from the portal circulation into the systemic circulation. The CPSS may be intrahepatic or extrahepatic and results in liver hypoplasia and functional hepatic insufficiency. Surgery to attenuate the shunting vessel, thus re-directing hepatic portal blood flow to the liver, is the preferred treatment (Greenhalgh et al. 2014). There are several surgical techniques used to achieve partial or complete attenuation of both intrahepatic and extrahepatic CPSS in dogs including suture attenuation, cellophane banding, ameroid constrictor and coil embolisation (White et al. 1998, Youmans & Hunt 1998, Hunt & Hughes 1999, Hunt 2004, Kummeling et al. 2004, Mehl et al. 2007, Falls et al. 2013, Murphy et al. 2001, Winkler et al. 2003) but few studies compare techniques, resulting in a lack of evidence to recommend one treatment over another (Tivers et al. 2012, 2017).

Additionally, there is a limited number of studies reporting the medium- to long-term follow-up after surgical attenuation and those available have varied time frames of follow-up. The current available reports have examined various techniques and different clinical variables to assess the outcome and success; including liver function tests (ammonia, bile acids), imaging to detect persistent shunting (scintigraphy and ultrasound) and owner assessment (Smith et al. 1995, White et al. 1998, Hunt & Hughes 1999, Hunt 2004, Kummeling et al. 2004, Frankel et al. 2006, Mehl et al. 2007, Falls et al. 2013, Greenhalgh et al. 2014, Weisse et al. 2014, Winkler et al. 2014). Most studies assessing biochemical parameters as an outcome measure do not show a return to normal reference values (Bristow et al. 2017, Hunt et al. 1999; Lawrence et al. 1992), although those assessing owner outcome do show an apparent return to a "normal" quality of life. However, for this latter long-term outcome, most studies use a simple form of owner assessment based on the resolution of clinical signs and whether the dog receives on-going medical management (Smith et al. 1995, Mehl et al. 2007, Falls et al.

2013, Weisse et al. 2014, Greenhalgh et al. 2014). Based on the current published literature there appears to be a discrepancy in objective measures of outcome (biochemical changes) *versus* subjective outcome (owner perceived improvement using a brief assessment). Quality of life is an increasingly important outcome measure in both human and veterinary medicine (Fayers et al. 1997, Mellanby et al. 2003, Freeman et al. 2005, Wiseman-Orr et al. 2006, Budke et al. 2008, German et al. 2012) but it is a difficult entity to assess for several reasons. There is no standardised definition, with different studies assessing different aspects under the umbrella term of health-related quality of life (HRQoL) and an extra challenge in veterinary medicine, as for paediatric medicine, is the lack of self-report, meaning the assessment has to be made by a third party. Furthermore, assessment is particularly complicated in dogs with CPSS as it is a congenital condition, so affected dogs are unlikely to have ever been truly 'normal', making assessment of whether dogs have made a full recovery, or simply improved, challenging. It is therefore imperative to compare the results of any questionnaire involving CPSS dogs to a population of healthy dogs, so that an accurate, more global evaluation of outcome can be made. The use of a consistent and detailed owner outcome assessment tool, including consideration of quality of life in comparison to more detailed analysis of presence or absence of continued clinical signs, and comparing to a control population, would be invaluable as part of the long-term outcome measure in dogs with CPSS.

This study therefore had three main aims:

(i)   To develop a questionnaire for use in dogs with CPSS that would assess owner-estimated quality of life as well as presence or absence of clinical signs;

(ii)   To compare this direct quality of life score with a score designed to assess clinical signs in more depth;

(iii)   To compare these results to a control population of healthy dogs to assess the quality of recovery of CPSS dogs following surgical attenuation.

Materials and Methods

Recruitment of cases

Medical records were reviewed for all dogs that had undergone surgical attenuation of a single, extrahepatic (EHCPSS) or intrahepatic (IHCPSS) CPSS between January 2000-December 2012 at two centres (XX= centre 1, YY= centre 2). Attempts were made to contact the owners of these dogs by telephone, email or regular mail. Dogs were included if they had a partial or complete suture attenuation, had a minimum of 18 months follow-up post-operatively and were alive at the time of data collection.

Dogs were treated with either complete or partial suture attenuation depending on subjective and objective assessments of intra-operative portal hypertension as previously described (Kummeling et al. 2004, Lee et al. 2006, Cariou et al. 2009). At Centre 1, a polypropylene (Prolene)[a] ligature (size 2-0 to 3-0), was used to attenuate the shunts (full attenuation where possible), and a second surgery to perform full attenuation was recommended for all dogs that tolerated a partial attenuation at the first surgery. At Centre 2, 2-0 polyethylene terephthalate (Ethibond)[b] was used for attenuation in all dogs. Second surgeries if a full attenuation had not been achieved were not recommended if dogs had a good clinical response to the first surgery.

Data collected from the medical records included signalment, body condition score (BCS), surgery date(s), type of shunt (EHCPSS or IHCPSS), whether complete or partial shunt attenuation was performed, whether a second surgery was performed and, when known, the presence of on-going shunting in the form of persistent flow through the CPSS or the development of multiple acquired shunts (MAS).

Owners of a control population of healthy dogs were invited to complete the HRQoL questionnaire. Control dogs were selected of the same breed and approximate ages as

113 the CPSS population. Control dogs were recruited by contacting individual UK Kennel club

114 breed societies and telephoning owners to ask them to participate in the study, a small

115 number were recruited *via* Centre 1's intranet from pets owned by non-clinical staff.

116

117 ***Questionnaire development***

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119 The questionnaire was developed on the basis of previously published veterinary

120 questionnaires (Reid et al. 2013, Levan et al. 2013). A 'direct' QOL question was asked

121 using a 10cm visual analog scale (VAS) from "worst imaginable" to "best imaginable"

122 both before surgery and at long term follow up (Appendix 2). This was measured and

123 converted to give a QoL score out of 100.

124

125 For assessment of clinical signs, questions were developed on the basis of widely

126 accepted clinical signs associated with CPSS (Berent & Tobias 2012). For each clinical

127 sign, the frequency was recorded on a categorical scale from 'never' to 'daily'. From

128 these questions a CPSS score was developed, to assess frequency and severity of clinical

129 signs; signs were divided into three classes according to severity, with class 1 answers

130 multiplied by 3, class 2 by 2 and class 3 by 1. Classes were determined subjectively by

131 the authors, based on expert opinion (see Table 1) and multiplication numbers were

132 determined arbitrarily based on expert opinion and previous work in this field

133 (unpublished data). Consequently, greater CPSS scores represented a more severely

134 clinically affected dog, with the highest score achievable of 110

135

136 There were two parts to the questionnaire with Part 1 (Appendix 1) assessing variables

137 pre- operatively and Part 2 at long-term follow up post-operatively (Appendix 2). The

138 questionnaires also questions regarding general behaviour and the dogs willingness to

139 participate in 'normal' canine activities including play, interaction with owners and other

140 dogs and exercise. These questions were measured on a VAS scale from 'Not at all

141 willing' through to 'Could not be more willing'. In addition, a question on the dog's

142 activity level was asked on a VAS scale from 'Not active at all' through to 'Could not be

143 more active'. To capture the effect of CPSS on growth, owners were asked to report if

144 their dog was considered small or underweight for their breed and age, and whether their

145 body condition had changed since they acquired them. For further questionnaire design

146 see Addendum 1.

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148 The questionnaire was either filled out by the owner whilst attending a hospital follow-up

149 appointment for a concurrent study at Centre 1 (Bristow et al. 2017), or mailed or

150 emailed to the owners.

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152 ***Statistical analysis***

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154 Statistical analysis was performed using IBM SPPS Statistics v21. Continuous data were

155 assessed graphically for normality. Mean and standard deviation were reported for

156 normally distributed data and median and 25th-75th percentiles were reported for non-

157 normally distributed data. IHCPSS and EHCPSS dogs were analysed separately.

158 Differences between the EHCPSS and IHCPSS dogs at long-term follow-up *versus* the

159 control group were compared using the Mann-Whitney U test. Significance was set at

160 P<0.05. Statistical analysis was not performed using part 1 of the questionnaire (pre-

161 operative results), due to the extended owner recall time.

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164 **Results**

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166 ***Demographics***

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168 One hundred and twenty-three dogs met the inclusion criteria at Centre 1 and 132 at

169 Centre 2. Of these, 76 owners (61.8%) returned the questionnaire at Centre 1 and 52

170   (39%) at Centre 2; resulting in 128 study dogs. 108 dogs had an EHCPSS and 20 an

171   IHCPSS. Median follow up time was 64 months (range 19.7-157.2).

172   The most commonly represented breed in the EHCPSS group was the Yorkshire terrier

173   (n=14), followed by the miniature schnauzer (n=12), (Table 2). In the IHCPSS group,

174   golden retrievers (n=6), followed by Labrador retrievers (n=3) were the most commonly

175   represented (Table 3). The mean age at follow up for EHCPSS dogs was 84.9 months (±

176   37.2) and 74.8 months for IHCPSS dogs (± 28.7).

177   One hundred and thirty-one control dogs were recruited (including three dogs *via* Centre

178   1's intranet). In the control group, cross breeds were the most commonly represented

179   (n=13), followed by bichon frise (n=9), (Table 4). The mean age of the control dogs was

180   93.5 months (± 28.8).

181

182   ***Surgical treatment***

183   Seventy-one of 108 dogs with an EHCPSS (65.7%) had a full attenuation (in one or two

184   surgeries), with 35 dogs (32.4%) having a partial attenuation only (n=34 with

185   polyethylene terephthalate (Ethibond), n=1 with polypropylene (Prolene)), and two dogs

186   (2%) diagnosed with MAS; one following partial attenuation (detected at the second

187   surgery), and the second following a full attenuation (both with polypropylene).

188   Nine of 18 dogs with an IHCPSS (50%) had a complete attenuation (in one or two

189   surgeries, all with polypropylene (Prolene)), with nine dogs (50%) having a partial

190   attenuation (n=7 with polyethylene terephthalate (Ethibond), n=2 with polypropylene

191   (Prolene)). Two dogs (10%) developed MAS; one following partial attenuation (detected

192   at the second surgery), and the second following a full attenuation (both with

193   polypropylene (Prolene)).

194

195   At Centre 1, three dogs with MAS were receiving medical management with all three on a

196   low protein diet, one on lactulose and one receiving occasional antibiotics when the

197 owner felt 'he was not acting his usual self'. One dog that had been treated with a partial

198 attenuation was receiving antibiotics, lactulose and a low protein diet and a second

199 partially-attenuated CPSS dog was receiving a low protein diet. A final dog that had been

200 treated by complete attenuation was also on a low protein diet but the owner had

201 decided to continue this after surgery contrary to recommendations.

202 At Centre 2 no dogs were receiving medical management, all lactulose was discontinued

203 immediately after surgery and low protein diet was transitioned to a normal diet over 1

204 post-operative week.

205

206 ***Questionnaire Results***

207 Summaries of the results of the questionnaire for EHCPSS dogs, IHCPSS dogs and control

208 dogs are presented in tables 5-7 and Appendix 4.

209

210 ***QoL Score***

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212 The long-term median QoL score of dogs with an IHCPSS was 94 (83-97.5), which was

213 not significantly different from the control group at 93 (82-98) (P=0.782). The long-term

214 median QoL score of EHCPSS dogs was significantly greater than the control group

215 (p=0.015) at 96 (89-100) (Table 5). There was an increase in QoL score in both EHCPSS

216 and IHCPSS dogs from pre-operatively to long-term follow-up (Table 5).

217

218 ***CPSS Score***

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220 The long-term median CPSS score of the IHCPSS (9 (1-26)) and EHCPSS (3 (1-10)) dogs

221 were significantly worse than that of the control group (1 (0-3)), with these differences

222 being statistically siginficant (p=0.003 for IHCPSS and p<0.001 for EHCPSS). CPSS score

223   was improved at long-term follow-up in dogs with IHCPSS and EHCPSS compared to pre-

224   operatively, with the median percentage improvement in CPSS score from pre-

225   operatively to long term follow up 72.4% for dogs with IHCPSS, and 90.5% for dogs with

226   EHCPSS (Table 5).

227

228

229   **Discussion**

230   To our knowledge this is the first study to use a HRQoL questionnaire to assess long-term

231   outcome of surgical treatment of CPSS in dogs and to compare these results to a control

232   population.

233

234   Design of a HRQoL questionnaire allowed us to compare an overall owner reported

235   health-related outcome in the form of the CPSS score (severity and frequency of clinical

236   signs) with a direct QoL score. Previous studies of dogs treated for CPSS have relied on a

237   brief owner assessment and one of our aims was to try to develop a more accurate

238   assessment tool that takes into account these two important domains. A need for this

239   more thorough type of evaluation is highlighted in this study by owners reporting the

240   direct QoL to be excellent at long term follow up, and comparable to a control population,

241   despite both EHCPSS and IHCPSS groups having significantly worse CPSS scores than

242   control dogs at long-term follow up. Clearly, both the QoL and a CPSS score such as we

243   designed in this study are both necessary to provide complementary information to allow

244   a more accurate overall long-term assessment of owner-derived outcome.

245

246   The persistence of a relatively high CPSS score at follow-up, and one statistically higher

247   than a control population, despite an apparent clinical improvement (based on QoL

248   measurement), is a novel finding as it suggests that although surgery for partial or

249   complete attenuation is associated with an improvement in frequency and severity of

250   clinical signs, the majority of dogs undergoing CPSS attenuation do not go back to what

251   is considered "normal", when compared to a healthy control population. This potentially

252   means that some dogs are being undertreated. If dogs do indeed have persistent subtle

253   clinical signs then individuals may benefit from further treatment. The finding of a lack of

254   return to "normal" fits with studies assessing other methods of outcome, for example,

255   serum bile acid concentrations have been shown to not reduce to within reference

256   intervals in the long-term in the majority of dogs with a complete shunt attenuation

257   (Bristow et al. 2017). It is suggested that some dogs have continued microvascular

258   shunting following CPSS surgery due to concurrent microvascular dysplasia or primary

259   portal vein hypoplasia (PPVH) (O'Leary et al. 2014). O'Leary et al. (2014) proposed a

260   spectrum of disease in dogs with CPSS, which could explain why some of these dogs

261   have not returned to the baseline of "normal" on other tests from previous studies, as

262   well as clinically in our study. People with liver disease can suffer from minimal hepatic

263   encephalopathy (MHE) (Groeneweg et al. 1998, Shawcross et al. 2007), so that affected

264   individuals do not show obvious signs of hepatic encephalopathy (HE) but do have

265   significant abnormalities in neurophysiological performance and on psychometric testing

266   and this might also occur in dogs.

267

268   Further potential causes to be considered are that not all dogs in this study underwent

269   imaging or blood testing to assess if MAS, persistent shunting or other abnormalities

270   were present, and 32% of the EHCPSS cases had a partial attenuation without follow-up

271   to determine if they had progressed to a full attenutation. 93% of these cases were

272   attenuated partially with polyethylene terephthalate and it is therefore probable that

273   some of them had progressed to a full attenuation, as even with partial attenuation using

274   polypropylene, 25% have been shown to spontaneously progress to a full attenuation

275   (unpublished data). Nevertheless some of these 32% of cases could have persistent

276   shunting, thereby accounting for some of the results seen. Equally, the approximate rate

277   of persistent shunting due to MAS is relatively low for dogs treated with suture ligation

278   (Hottinger 1995, White 1998, Tivers et al. 2017) and on balance, this population here

279   reflects standard clinical practice in many hospitals, of a combination of partial and

280   complete attenuation achieved, thereby providing useful information in a large population

281   of surgically teated dogs at follow up.

282

283   Despite the discrepancy in QoL score and CPSS score, encouragingly, our data does also

284   support the suggestion that suture attenuation of a CPSS results in a clinical

285   improvement, with an improved CPSS score for both EHCPSS and IHCPSS from pre-

286   operatively compared to long-term follow up - use of this questionnaire prospectively

287   (*i.e.* before and after surgery), will be able to provide statistical analysis on this

288   improvement in the future.

289

290   It is important to consider the limitations of owner based questionnaires, including

291   attention bias, meaning that owners notice and remember 'abnormal' episodes more

292   regularly, which could account for some of the difference in CPSS score, recall bias is

293   another potential limitation to owner based assessment and owners of affected dogs may

294   be more generous in their assessment of QoL compared to owners of "normal" dogs, as

295   they have seen such a dramatic improvement after receiving treatment – as evidenced

296   by the statistically better QoL observed by owners of CPSS dogs. Despite these

297   limitations, HRQoL is becoming increasingly recognised as a very important factor for

298   outcome measurement, with the emerging view in human medicine that it is an essential

299   assessment to consider when measuring treatment success (Garratt et al. 2002).

300

301   Design of a CPSS score was novel and based on expert opinion as has been the basis of

302   designing questionnaires in other studies (Reid et al. 2013, Freeman et al. 2013).

303   Naturally there will be differing expert opinions as to the impact of different clinical signs

304   on quality of life, but this questionnaire was designed as a starting point to begin more

305   in-depth analysis of outcome of CPSS dogs after treatment, leading on to future

306   improvement in this assessment as well as the ability to compare different techniques in

307   the future. As discussed in the introduction, there is a lack of evidence to currently

308   recommend one treatment over another (Tivers et al. 2012, 2017), and we should be

309 striving to improve the evidence, with the use of validated instruments for comparisons.

310 One of the strengths of this study is the availability of long-term information in a large

311 number of dogs, which is often time-consuming and difficult to collect but essential in

312 order to evaluate outcome of a condition and an intervention properly. It is hoped that

313 use of a consistent HRQoL questionnaire tool for CPSS dogs will make this important on-

314 going task more manageable, easier to compare between different institutions, with a

315 further benefit that it does not require the dog to return for a visit, blood test, sedation

316 or anaesthesia, or imaging investigations.

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318

319 **Footnotes**

320 a. Prolene, Ethicon Ltd, Edinburgh, UK.

321 b. Ethibond, Johnson & Johnson Medical BV, Amersfoort, NL.

322
323 No conflicts of interest have been declared
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