TITLE: Health-related quality of life following surgical attenuation of congenital portosystemic shunts versus healthy controls

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Health Related Quality of Life following Surgical Attenuation of Congenital Portosystemic Shunts versus Healthy Controls

Summary

Objectives: To design a health-related quality of life questionnaire for dogs with congenital portosystemic shunts, use this in a cohort of dogs treated with suture attenuation and compare results with that from a healthy control cohort.

Methods: Data were collected from the hospital records of dogs treated with suture ligation of an intrahepatic or extrahepatic congenital portosystemic shunt at two referral centres. Owners were asked to complete a questionnaire assessing their dog's health-related quality of life pre-operatively (retrospectively) and at the time of follow-up. Owners of control dogs also completed the questionnaire.

Results: 128 dogs with congenital portosystemic shunts and 131 control dogs were recruited. Median follow-up time was 64 months (range 19.7-157.2). The median long-term health-related quality of life score was excellent for both intrahepatic (94/100) and extrahepatic (96/100) shunt cases and similar to that of control dogs. The long-term median CPSS scores of both IHCPSS and EHCPSS dogs were significantly worse than the control group.

Clinical significance: Suture attenuation of congenitial portosystemic shunts is associated with an excellent health-realted quality of life score at long-term follow-up.

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

the CPSS population. Control dogs were recruited by contacting individual UK Kennel club breed societies and telephoning owners to ask them to participate in the study, a small number were recruited *via* Centre 1's intranet from pets owned by non-clinical staff.

Questionnaire development

The questionnaire was developed on the basis of previously published veterinary questionnaires (Reid et al. 2013, Levan et al. 2013). A 'direct' QOL question was asked using a 10cm visual analog scale (VAS) from "worst imaginable" to "best imaginable" both before surgery and at long term follow up (Appendix 2). This was measured and converted to give a QoL score out of 100.

For assessment of clinical signs, questions were developed on the basis of widely accepted clinical signs associated with CPSS (Berent & Tobias 2012). For each clinical sign, the frequency was recorded on a categorical scale from 'never' to 'daily'. From these questions a CPSS score was developed, to assess frequency and severity of clinical signs; signs were divided into three classes according to severity, with class 1 answers multiplied by 3, class 2 by 2 and class 3 by 1. Classes were determined subjectively by the authors, based on expert opinion (see Table 1) and multiplication numbers were determined arbitrarily based on expert opinion and previous work in this field (unpublished data). Consequently, greater CPSS scores represented a more severely clinically affected dog, with the highest score achievable of 110

There were two parts to the questionnaire with Part 1 (Appendix 1) assessing variables pre- operatively and Part 2 at long-term follow up post-operatively (Appendix 2). The questionnaires also questions regarding general behaviour and the dogs willingness to participate in 'normal' canine activities including play, interaction with owners and other dogs and exercise. These questions were measured on a VAS scale from 'Not at all willing' through to 'Could not be more willing'. In addition, a question on the dog's

activity level was asked on a VAS scale from 'Not active at all' through to 'Could not be more active'. To capture the effect of CPSS on growth, owners were asked to report if their dog was considered small or underweight for their breed and age, and whether their body condition had changed since they acquired them. For further questionnaire design see Addendum 1.

The questionnaire was either filled out by the owner whilst attending a hospital follow-up appointment for a concurrent study at Centre 1 (Bristow et al. 2017), or mailed or emailed to the owners.

Statistical analysis

Statistical analysis was performed using IBM SPPS Statistics v21. Continuous data were assessed graphically for normality. Mean and standard deviation were reported for normally distributed data and median and 25^{th}-75^{th} percentiles were reported for non-normally distributed data. IHCPSS and EHCPSS dogs were analysed separately. Differences between the EHCPSS and IHCPSS dogs at long-term follow-up *versus* the control group were compared using the Mann-Whitney U test. Significance was set at $P<0.05$. Statistical analysis was not performed using part 1 of the questionnaire (pre-operative results), due to the extended owner recall time.

Results

Demographics

One hundred and twenty-three dogs met the inclusion criteria at Centre 1 and 132 at Centre 2. Of these, 76 owners (61.8%) returned the questionnaire at Centre 1 and 52

(39%) at Centre 2; resulting in 128 study dogs. 108 dogs had an EHCPSS and 20 an IHCPSS. Median follow up time was 64 months (range 19.7-157.2).

The most commonly represented breed in the EHCPSS group was the Yorkshire terrier (n=14), followed by the miniature schnauzer (n=12), (Table 2). In the IHCPSS group, golden retrievers (n=6), followed by Labrador retrievers (n=3) were the most commonly represented (Table 3). The mean age at follow up for EHCPSS dogs was 84.9 months (± 37.2) and 74.8 months for IHCPSS dogs (± 28.7).

One hundred and thirty-one control dogs were recruited (including three dogs *via* Centre 1's intranet). In the control group, cross breeds were the most commonly represented (n=13), followed by bichon frise (n=9), (Table 4). The mean age of the control dogs was 93.5 months (± 28.8).

Surgical treatment

Seventy-one of 108 dogs with an EHCPSS (65.7%) had a full attenuation (in one or two surgeries), with 35 dogs (32.4%) having a partial attenuation only (n=34 with polyethylene terephthalate (Ethibond), n=1 with polypropylene (Prolene)), and two dogs (2%) diagnosed with MAS; one following partial attenuation (detected at the second surgery), and the second following a full attenuation (both with polypropylene).

Nine of 18 dogs with an IHCPSS (50%) had a complete attenuation (in one or two surgeries, all with polypropylene (Prolene)), with nine dogs (50%) having a partial attenuation (n=7 with polyethylene terephthalate (Ethibond), n=2 with polypropylene (Prolene)). Two dogs (10%) developed MAS; one following partial attenuation (detected at the second surgery), and the second following a full attenuation (both with polypropylene (Prolene)).

At Centre 1, three dogs with MAS were receiving medical management with all three on a low protein diet, one on lactulose and one receiving occasional antibiotics when the

owner felt 'he was not acting his usual self'. One dog that had been treated with a partial attenuation was receiving antibiotics, lactulose and a low protein diet and a second partially-attenuated CPSS dog was receiving a low protein diet. A final dog that had been treated by complete attenuation was also on a low protein diet but the owner had decided to continue this after surgery contrary to recommendations.

At Centre 2 no dogs were receiving medical management, all lactulose was discontinued immediately after surgery and low protein diet was transitioned to a normal diet over 1 post-operative week.

Questionnaire Results

Summaries of the results of the questionnaire for EHCPSS dogs, IHCPSS dogs and control dogs are presented in tables 5-7 and Appendix 4.

QoL Score

The long-term median QoL score of dogs with an IHCPSS was 94 (83-97.5), which was not significantly different from the control group at 93 (82-98) (P=0.782). The long-term median QoL score of EHCPSS dogs was significantly greater than the control group (p=0.015) at 96 (89-100) (Table 5). There was an increase in QoL score in both EHCPSS and IHCPSS dogs from pre-operatively to long-term follow-up (Table 5).

CPSS Score

The long-term median CPSS score of the IHCPSS (9 (1-26)) and EHCPSS (3 (1-10)) dogs were significantly worse than that of the control group (1 (0-3)), with these differences being statistically siginficant (p=0.003 for IHCPSS and p<0.001 for EHCPSS). CPSS score

was improved at long-term follow-up in dogs with IHCPSS and EHCPSS compared to pre-operatively, with the median percentage improvement in CPSS score from pre-operatively to long term follow up 72.4% for dogs with IHCPSS, and 90.5% for dogs with EHCPSS (Table 5).

Discussion

To our knowledge this is the first study to use a HRQoL questionnaire to assess long-term outcome of surgical treatment of CPSS in dogs and to compare these results to a control population.

Design of a HRQoL questionnaire allowed us to compare an overall owner reported health-related outcome in the form of the CPSS score (severity and frequency of clinical signs) with a direct QoL score. Previous studies of dogs treated for CPSS have relied on a brief owner assessment and one of our aims was to try to develop a more accurate assessment tool that takes into account these two important domains. A need for this more thorough type of evaluation is highlighted in this study by owners reporting the direct QoL to be excellent at long term follow up, and comparable to a control population, despite both EHCPSS and IHCPSS groups having significantly worse CPSS scores than control dogs at long-term follow up. Clearly, both the QoL and a CPSS score such as we designed in this study are both necessary to provide complementary information to allow a more accurate overall long-term assessment of owner-derived outcome.

The persistence of a relatively high CPSS score at follow-up, and one statistically higher than a control population, despite an apparent clinical improvement (based on QoL measurement), is a novel finding as it suggests that although surgery for partial or complete attenuation is associated with an improvement in frequency and severity of clinical signs, the majority of dogs undergoing CPSS attenuation do not go back to what is considered “normal”, when compared to a healthy control population. This potentially

means that some dogs are being undertreated. If dogs do indeed have persistent subtle clinical signs then individuals may benefit from further treatment. The finding of a lack of return to "normal" fits with studies assessing other methods of outcome, for example, serum bile acid concentrations have been shown to not reduce to within reference intervals in the long-term in the majority of dogs with a complete shunt attenuation (Bristow et al. 2017). It is suggested that some dogs have continued microvascular shunting following CPSS surgery due to concurrent microvascular dysplasia or primary portal vein hypoplasia (PPVH) (O'Leary et al. 2014). O'Leary et al. (2014) proposed a spectrum of disease in dogs with CPSS, which could explain why some of these dogs have not returned to the baseline of "normal" on other tests from previous studies, as well as clinically in our study. People with liver disease can suffer from minimal hepatic encephalopathy (MHE) (Groeneweg et al. 1998, Shawcross et al. 2007), so that affected individuals do not show obvious signs of hepatic encephalopathy (HE) but do have significant abnormalities in neurophysiological performance and on psychometric testing and this might also occur in dogs.

Further potential causes to be considered are that not all dogs in this study underwent imaging or blood testing to assess if MAS, persistent shunting or other abnormalities were present, and 32% of the EHCPSS cases had a partial attenuation without follow-up to determine if they had progressed to a full attenutation. 93% of these cases were attenuated partially with polyethylene terephthalate and it is therefore probable that some of them had progressed to a full attenuation, as even with partial attenuation using polypropylene, 25% have been shown to spontaneously progress to a full attenuation (unpublished data). Nevertheless some of these 32% of cases could have persistent shunting, thereby accounting for some of the results seen. Equally, the approximate rate of persistent shunting due to MAS is relatively low for dogs treated with suture ligation (Hottinger 1995, White 1998, Tivers et al. 2017) and on balance, this population here reflects standard clinical practice in many hospitals, of a combination of partial and

complete attenuation achieved, thereby providing useful information in a large population of surgically teated dogs at follow up.

Despite the discrepancy in QoL score and CPSS score, encouragingly, our data does also support the suggestion that suture attenuation of a CPSS results in a clinical improvement, with an improved CPSS score for both EHCPSS and IHCPSS from pre-operatively compared to long-term follow up - use of this questionnaire prospectively (*i.e.* before and after surgery), will be able to provide statistical analysis on this improvement in the future.

It is important to consider the limitations of owner based questionnaires, including attention bias, meaning that owners notice and remember 'abnormal' episodes more regularly, which could account for some of the difference in CPSS score, recall bias is another potential limitation to owner based assessment and owners of affected dogs may be more generous in their assessment of QoL compared to owners of "normal" dogs, as they have seen such a dramatic improvement after receiving treatment – as evidenced by the statistically better QoL observed by owners of CPSS dogs. Despite these limitations, HRQoL is becoming increasingly recognised as a very important factor for outcome measurement, with the emerging view in human medicine that it is an essential assessment to consider when measuring treatment success (Garratt et al. 2002).

Design of a CPSS score was novel and based on expert opinion as has been the basis of designing questionnaires in other studies (Reid et al. 2013, Freeman et al. 2013). Naturally there will be differing expert opinions as to the impact of different clinical signs on quality of life, but this questionnaire was designed as a starting point to begin more in-depth analysis of outcome of CPSS dogs after treatment, leading on to future improvement in this assessment as well as the ability to compare different techniques in the future. As discussed in the introduction, there is a lack of evidence to currently recommend one treatment over another (Tivers et al. 2012, 2017), and we should be

striving to improve the evidence, with the use of validated instruments for comparisons. One of the strengths of this study is the availability of long-term information in a large number of dogs, which is often time-consuming and difficult to collect but essential in order to evaluate outcome of a condition and an intervention properly. It is hoped that use of a consistent HRQoL questionnaire tool for CPSS dogs will make this important on-going task more manageable, easier to compare between different institutions, with a further benefit that it does not require the dog to return for a visit, blood test, sedation or anaesthesia, or imaging investigations.

Footnotes

a. Prolene, Ethicon Ltd, Edinburgh, UK.

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

No conflicts of interest have been declared

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