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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2019 16(1):234-241. **OPEN ACCESS**

The prognostic value of electrocardiography for canine parvo virus infection in German shepherd puppies

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Canine parvovirus type 2 (CPV-2) is the most common cause of puppies mortality in first 6 months. However, no established specific prediction study was done within special breed. The purpose of this study was to evaluate the prognostic usefulness of epidemiological, hemato-biochemical and electrocardiogram (ECG) findings in German shepherd puppies with canine parvovirus (CPV). Twenty-two puppies (11 male, 11 female) were used in the study. All puppies were underwent a complete physical examination, Commercial canine parvo kit, laboratory variables (CBC, ALT, creatnine, Na, K, Ca, CPK-mb, cTn-I) and ECG then treated according to treatment protocol with following up every day till recovery or death. Mortality rate among these puppies was twenty-seven percent. Non-survivors were younger and had significantly lower platelet counts, serum potassium concentrations and T- wave length than those puppies who survive at presentation ($p<0.05$). Serum cTn-I were positive in only seventeen percent of non-survival dogs while there was only six percent of the survival dogs showed positive cTn-I. This study suggested that age, platelet count, serum potassium, and T-wave length are useful for predicting the final outcome of hospitalized German shepherd puppies with CPV.

Keywords: Canine parvovirus, cTn-I, prognosis, ECG.

INTRODUCTION

Canine parvovirus type 2 (CPV-2) one of the most important viruses infecting dogs causing high morbidity and often mortality, especially in puppies between 6 weeks and 6 months but this parameter failed to achieve significance (Ling et al., 2012; Decaro et al., 2007; Markovich et al., 2012; Nandi et al., 2013; Miranda et al., 2015; Mylonakis et al., 2016; Dossin et al., 2011). Despite the presence of vaccine, still morbidity and mortality remain a huge problem in dog populations worldwide, (Hoskins, 1993; Carmichael, 2005).

German shepherd, rottweiler, doberman pinscher, American pit bull terrier, Labrador retriever and Yorkshire terrier appear to be more prone to severe CPV enteritis than other breeds (Houston et al., 1996; McCaw and Hoskins 2006). However, no cumulative evidence that differences in breed-specific; immune competence, vaccine unresponsiveness play a role in expression of CPV enteritis in these breads (Schoeman et al., 2013) .

The disease can come in three different forms; intestinal form, cardiac form associated with sudden death and finally generalized focal necrotic form in 2 weeks old puppies (Lenghaus and Studdert, 1984).

However, Myocarditis associated with CPV-2 infection is suggested to be either connected with effect of CPV itself or as a consequence to sepsis (Carpenter et al., 1980; Vortel et al., 1982;

Lenghaus and Studdert, 1984; Meunier et al., 1984; Van Rensburg and Meintjes, 1986; Agungpriyono et al., 1999; Atwell and Kelly, 2008).

Some serum biochemical parameter could give an idea about myocardial injury. Classically, creatine kinase (CK), a wide known cardiac biomarker, might be used for perlimenary detection of muscle injury and consequently myocardial injury, although the value of CK is questionable due to lack of tissue specificity and sensitivity (Schober et al., 2002; Qi and Sun, 2004; O'Brien, 2008; Franco et al., 2009).

Nowadays, Cardiac troponin I (cTnI) is considered an ultimate biomarker for recognition of myocardium injury in humans and dogs (Schober et al., 1999, 2002; Rosalki et al., 2004; Walker, 2006; Babuin and Jaffe, 2005; Apple et al., 2008), also the elevation in serum cTnI connected with cardiac morphologic alterations (Apple et al., 2008).

This investigation aimed to study prognostic value of cardiac biomarkers (CK-MB and cTnI), ECG parameters as well as hemato-biochemical parameters in naturally CPV-infected German shepherd through establishing a statistical prediction model based on obtained data.

MATERIALS AND METHODS

Selection of animals

German shepherd dogs of both genders (11 male, 11 female) and different ages with hemorrhagic gastroenteritis presented between October 2016 and October 2017 at private Small Animal clinic with in-patient facility near Giza, Egypt are subjected to clinical examination. These dogs were not submitted to any veterinary clinic or take any treatment before being admitted to our facility. Dogs were suffering from vomiting and bloody diarrhea and positive for Canine parvo enteritis (PVE) using commercial rapid kit (Antigen Rapid CPV Kit, Animal genetics, Inc., Korea).

Study design

According to treatment response, dogs with PVE were further subdivided into two groups for the purpose of analysis: survival and non-survival dogs. At admission, Skin tenting test, mucous membrane and capillary refilling time (CRT) were used to evaluate dehydration and hypo perfusion within each dog and to accurately calculate fluid therapy doses and type. Fecal examination was done to exclude complicating agent as toxocara canis or isospora spp.. Venous blood samples were collected after rehydration of suffering animals into two vacutainer tubes, the first one with ethylene-diamine-tetra-acetic acid (EDTA) for CBC and the second one with separation gel for serum biochemical analysis.

Type of fluid therapy, rate and route was set to each case individually and updated each day according to the dehydration and in-going losses according to (Davis et al., 2013).

The antibiotic therapy consisted of amoxicillin / clavulinic acid (20 mg/kg IV every 8 hours) then aminoglucosides (amikacin, 20 mg/kg IV, Intramuscularly once daily) is added after correction of dehydration. Metronidazole(15–20 mg/kg by mouth every 12 hours for up to 10 days) used to treat anaerobic bacteria, Anti emetic (Ondansetron, 0.11 mg/kg slow i/v every 12 hours) to control intractable vomiting, h2 blockers (rantidine 2 mg/kg s/c every 12 hours) to control gastric secretion consequently decrease gastric irritation. (Plumb, 2008**;** Goddard & Leisewitz, 2010; Boag, 2013; Sen et al., 2014).

Selected epidemiological data (age, sex, weight, season), haematological findings, and biochemical parameters (ALT, Creatnine, Na, Ca, K, CPK-mb , Cardiac Troponin-I "cTnI") were done on all cases. Additionally, electrocardiogram was done in right lateral recumbancy in the first day of admission and ECG parameters were used to produce a model that predicts survival of PVE-infected German shepherds.

Statistical methodology

Simple student T-test was conducted to compare means between numerical data of survivors and non-survivors. Meanwhile; categorical data was submitted to chi-square test to see if there is any significant difference between two groups (SPSS Inc).

All parameter were included in attempt to create a prediction model using two systems Logistic Regression and Discriminant. Initially, the association between each variable and the final outcome was evaluated in univariable conditional logistic regression models. All that were significant at the 5% level in the likelihood ratio test were used in the model. Subsequently, their two-way interactions were created and evaluated for significance at the 5% level in likelihood ratio tests. (Dohoo et al., 2003)

RESULTS

German shepherd dogs with age ranged from 1 to 4 months and of both sexes, suffering from parvo-virus enteritis (PVE).

Table 1 : Age and weight difference between both survivors and non-survivors PVE infected dogs (mean values ± SE)

	Non-survivors		survivors		Significance
Parameter	Mean	St. error	Mean	St. error	
Age (days)	64.17	±7.90	95.00	±5.16	0.005
Weight (kg)	5.83	±1.58	9.31	±0.91	0.06

Table 2 : Hematological parameters of both survivors and non-survivors PVE infected dogs (mean values ± SE)

	Non-survivors		survivors		Significance
Parameter	Mean	St. error	Mean	St. error	
RBCs (*10^6 /ml)	5.11	± 0.54	5.79	±0.37	0.32
PCV (%)	35.12	± 2.56	36.21	±1.94	0.76
Hb (gm/dl)	11	± 0.84	11.76	±0.57	0.48
MCV (fl)	71.27	± 7.36	62.99	±1.11	0.31
MCH (pg)	22.08	± 1.60	20.55	±0.34	0.39
MCHC (%)	31.35	± 0.83	32.69	±0.55	0.21
WBCs (cell /ml)	12508	± 2479	9894	±1281	0.32
Nutrophils (cell /ml)	6097	± 1447	5250	±816	0.60
Band cell (cell /ml)	378	± 101	270	±42	0.36
Lymphocytes (cell /ml)	4301	± 1217	2776	±447	0.28
Monocytes (cell /ml)	1490	± 455	1425	±194	0.88
Esinophils (cell /ml)	240	± 70	162	±26	0.34
Basophils (cell /ml)	0.00	± 0.00	9.24	±9.24	0.55
Platelets (*10^3 /ml)	137.17	± 40.00	245.19	±28.51	0.05

Table 3 : biochemical parameters of both survivors and non-survivors PVE infected dogs (mean values ± SE)

	Non-survivors		survivors		Significance
Parameter	Mean	St. error	Mean	St. error	
ALT (U/L)	57.33	±16.74	60.13	±14.73	0.92
Creatnine (mg/dl)	0.68	±0.07	0.70	±0.05	0.86
Ca (mg/dl)	9.67	±0.54	9.94	±0.28	0.64
Na (mEq/L)	142.67	±0.95	143.14	±0.88	0.75
K (mEq/L)	4.43	±0.35	5.10	±0.13	0.04
CPKmb (IU/L)	114.51	±75.38	63.86	±32.11	0.47

Table 4 : electrocardiographic parameters of both survivors and non-survivors PVE infected dogs (mean values ± SE)

	Non-survivors		survivors		Significance
Parameter	**Mean**	**St. error**	**Mean**	**St. error**	
P width (second)	0.03	±0.01	0.03	±0.01	0.89
P length (Mv)	0.12	±0.03	0.14	±0.02	0.61
Qrs width (second)	0.04	±0.00	0.04	±0.00	0.54
Qrs length (Mv)	0.90	±0.21	1.81	±0.29	0.08
PR interval (second)	0.06	±0.01	0.06	±0.01	0.83
St segment (second)	0.11	±0.01	0.12	±0.01	0.51
T width (second)	0.09	±0.01	0.08	±0.01	0.68
T length (Mv)	0.13	±0.02	0.30	±0.04	0.02

Dogs were divided according to final outcome into 16 survivors (73%) and 6 non-survivors (27%). Fifty- six percent (56%) of Survivors were females and 44% were males while 67 % of dead dogs were males. Majority of cases acquire CPV infection during autumn season (16 out of 22).

Age (survivors 95 day, non- survivors 64 day, P= 0.005) was the most important epidemiologic factor. While weight (survivors 9.31 kg, non-survivors 5.83 kg, P = 0.06) showed non-significant difference. Table (1)

On clinical examination of the 22 cases, they were observed to have fever or normal rectal temperature and moderate to severe anemia.

Hemato-biochemical examination of studied cases showed only significant difference between means of the two groups in: platelets (survivors = 245.19* 10^3 cell/mm, non- survivors 137.17* 10^3 cell/mm, P= 0.05) and potassium (survivors 5.10 mEq/L , non- survivors 4.43 mEq/L, P= 0.04) Table (2,3)

Regarding ECG finding, sinus tachycardia was the most encountered rhythm (14 case, 64%). T wave length was significantly different between groups (survivors 0.30 Mv, non-survivors 0.13 Mv, P = 0.02) but the difference in QRS wave length failed to gain significance (survivors 1.81 Mv, non- survivors 0.90 Mv, P = 0.08). Table (4)

Cardiac Troponin I (cTnI) was positive only for 17% of non-survivors and 6% of survived dogs (P= 0.45). Non of categorical data (sex, season, cTnI and ECG rythem) used in chi- square test showed significance.

Regarding model designing, only platelets give an acceptable univariable conditional logistic regression model, but none of other multi-variates models were significant.

DISCUSSION

Parvo viral enteritis (PVE) was reported in high frequency within certain breeds like Rottweilers, Doberman Pinschers, English Springer Spaniels, American Pit Bull Terriers and German shepherd dogs (Glickman et al., 1985; Houston et al., 1996). But according to our knowledge none of previous prognostic studies try to make a breed specific model.

Current result showed that gender had no influence in the CPV-favorable outcome. Previous studies (Miranda et al., 2015 ; Godsall et al., 2010) results approved that too, while Houston et al., (1996) stated that males had less favorable prognosis than females

Recorded case fatality rate was 27% which agree with previous studies that ranged it between 25% and 35% (Brinke and Neiger, 2010; Glickman et al., 1985; Horner, 1983; Kalli et al., 2010). On the other hand, ling et al. (2012) estimated fatality rate 42.3%, and higher than Otto et al., (1997 and 2001) who stated that survival rate was more than 90% in puppies treated in tertiary care veterinary facilities

Among PVE cases, there is no significant difference for season-related increase of deaths in contrast with previous data which suggest that season of diagnosis (summer) was significantly associated increase of fatal outcome (ling et al., 2012).

Young age and low body weight were usually encountered among non- survivor puppies but only the age was significant at 95% confidence rate. These result conceded with Good and Otto, (2006); Dossin et al., (2011) and Schoeman et al., (2013) who mentioned that Low bodyweight was a potential risk factor for death even if it is age adjusted. Unlike surprising finding of ling et al.,

(2012) that suggest no age related influence on case fatality.

Canine parvo enteritis is known to destruct the haematopoietic progenitor cells causing several hematological changes. In current study, there was no significant variation between groups in any of complete blood count variables except platelets.

These finding contrary to previous one of Schoeman et al., (2013) who found that lack of leucocytopenia and lymphopenia one day post-admission was highly suggestive for survival in CPV infected puppies. Other authors predict that on-admission leucocyte count (total and differential) is lower in Non-survivors compared to survivors (Mason et al., 1987; Dossin et al., 2011; Yilmaz and Senturk 2007).

But in this study, Non-survivors have slightly higher leucocytic count and lymphocytic count this may attribute to transient nature of leucopenia associated with canine parvo enteritis (Macartney et al., 1984; Goddard et al., 2008; Ling et al., 2012). Higher leukocyte count in dead puppies may be explained by systemic inflammatory response syndrome (SIRS) associated with canine parvo enteritis which have poor prognosis (kalli et al., 2010)

Another study Glickman et al., (1985) found that there is no association between survivability and leukopenia at the time of admission.

In current study thrombocytopenia associated with risk of death of canine parvovirus puppies. PVE-associated thrombocytopenia can result from decrease of platelet production or as a consequence of direct destruction by viruses or immunologic components on platelets or vascular endothelium (Wilson et al. 1982). Poor prognosis may be attributed to platelet effect on vascular permeability potentiating further extravascular dissemination of canine viral diseases like canine distemper (Axthelm and Krakowka, 1987).

Concerning biochemical finding, potassium is lower significantly in non-survivors compared to survived puppies. While ALT, creatnine, Na and Ca levels don't show any significance between groups.

Decrease of serum potassium levels is attributed to ceased dietary intake and increased loss via vomiting and diarrhea, and manifested clinically by depression and muscle weakness. (Nappert et al. 2002; Ettinger and Feldman 2010).

Cardiac Troponin I (cTnI) and CPK-mb, as cardiac muscle biomarkers, are proteins present in cardiac myocytes and leak into blood circulation through damaged cell membrane. Its serum levels are aid in diagnosis of myocardial affection as well as monitoring treatment progress in veterinary medicine (Schober et al., 2002; Qi and Sun, 2004; Diniz et al., 2007; Franco et al., 2009).

Kocaturk et al., (2012) found no prognostic value of CPK in contrast to cTnI that elevate in non survivors compared to survivors in opposite to our study in which none of them is prognostic.

ECG is usually used as a preliminary diagnostic to evaluate heart diseases, but it is not precise in revealing cardiac myocyte injure in dogs (Miller et al., 1999). In this study smaller T wave associated with poor prognosis and to a lesser extent low QRS amplitude but failed to gain significance. Previous studies established a link between decreased QRS amplitude and dogs with sepsis (Yilmaz et al., 1997) and it is believed that Myocardial dysfunction one of the most important consequensis of sepsis in dogs (Otto, 2007) and Small QRS wave was seen in PVE dogs with sub acute myocarditis (Robinson et al., 1979) . In contrary Kocaturk et al., (2012) reported that there no significant prognostic finding on ECG but dogs with PVE most likely to have sinus tachycardia as in current study. This sinus tachycardia could be explained by cardiac muscle destruction or its response to metabolic disturbance commonly happened with PVE. (Yilmaz et al., 1997; Miller et al., 1999)

CONCLUSION

In conclusion; Survivability could be predicted through Electrocardiogram (ECG) finding especially T wave length, hemato-biochemical parameter (platelet and potassium) and finally from age of diseased animal.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

Authors like to expose great gratitude to laboratory of internal medicine, faculty of veterinary medicine, Cairo university

AUTHOR CONTRIBUTIONS

AA and IA designed the experiment. SI, FA and ME wrote the manuscript. ME performed clinical examination and ECG. ME, SI performed hematological and biochemical examinations. ME, SI analyzed the data. All authors interpreted the data, revised and approved the final version.

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