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Research Article

Clinical and Haematological Findings in Bovine Immunodeficiency Virus (BIV) Infected Cattle

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Abstract: The clinical and haematological findings in dairy cattle with naturally infected bovine immunodeficiency virus (BIV) infection were evaluated. Thirty-seven (12.3%) out of 300 cattle that had previously been found positive for BIV infection were monitored. Thirty-seven BIV-free cattle selected from BIV-positive herds were used as a control group. Routine clinical and haematological parameters were recorded 6 times, at 1-month intervals.

Mastitis (n = 18), metritis (n = 9), respiratory system diseases (n = 8), retained placenta (n = 7), and regional lymphadenopathy (n = 7) were predominantly diagnosed during the monitoring period in BIV-infected cattle, and mastitis (n = 1) and metabolic disturbance (n = 1) in the control animals. Heart and respiratory rates were significantly higher ($P < 0.01$) in BIV-infected cattle than in the control group. White blood cell (WBC) count and lymphocyte rate were lower ($P < 0.01$) in BIV-infected cattle, but the neutrophil rate was higher ($P < 0.05$) than those of the control group. There were no significant differences in erythrocyte or platelet indices within or between the groups during the study.

These findings suggest that the presence of BIV infection should be considered a health risk to cattle populations, and may have a role in changing WBC and differential cell counts in the host.

Key Words: Bovine immunodeficiency virus, BIV, clinical disorders, blood parameters, cattle

Sığır İmmun Yetmezlik Virusu (BIV) ile Enfekte Sığırlarda Klinik ve Hematolojik Bulgular

Özet: Sunulan bu çalışmada sığır immun yetmezlik virusu (BIV) ile dogal enfekte süt sığırlarının klinik ve hematolojik bulguları değerlendirildi. Üç yüz sığır arasından BIV enfeksiyonu yönünden pozitif bulunan 37 sığır (% 12,3) değerlendirmeye alındı. BIV pozitif sürülerden seçilen BIV negatif 37 sığır kontrol grubu olarak kullanıldı. Rutin klinik ve hematolojik parametreler bir ay arayla altı kez kaydedildi.

Gözlem sürecinde, BIV ile enfekte sığırlarda öncelikli olarak mastitis (n = 18), metritis (n = 9), solunum sistemi hastalıkları (n = 8), retentio secundinarum (n = 7), ve bölgesel lenfadenopati (n = 7), kontrol grubunda ise mastitis (n = 1) ve metabolik hastalıklar (n = 1) tanımlandı. BIV ile enfekte sığırların kalp ve solunum sayıları kontrol grubuna göre anlamlı düzeyde ($P < 0,01$) yüksek bulundu. Kontrol grubu ile karşılaştırıldığında, BIV ile enfekte sığırlarda total lökosit ve lenfosit sayısı daha düşük ($P < 0,01$), buna rağmen nötrofil oranları daha yüksek ($P < 0,05$) belirlendi. Çalışma sürecinde grup içi ve gruplar arasında eritrosit ve trombosit indekslerinde istatiksel farklılık belirlenemedi.

Bu bulgular BIV enfeksiyonunun sığır populasyonu için bir sağlık riski oluşturabileceğini ve konakçıda total lökosit ve formül lökosit sayılarının değişiminde rol oynayabileceğini göstermektedir.

Anahtar Sözcükler: Sığır immun yetmezlik virusu, BIV, klinik bozukluklar, kan parametreleri, sığır

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Introduction

Bovine immunodeficiency virus (BIV) is classified in the genus lentivirus, of the family Retroviridae (1-6). However, lentiviruses in general are transmitted both horizontally and vertically and the route and mechanism of natural transmission in cattle are largely unknown (5,7,8). Serological investigations have shown wide distribution with differing prevalence (1.4% to 80%) of BIV infections around the world (1-7).

Although several pathological changes have been reported in BIV-infected cattle, including monocyte dysfunction, encephalopathy, lymphadenopathy, and immunodeficiency, the detailed pathogenesis of BIV-infected cattle remains unclear (1-7,9). Given the similarity of this virus to human immunodeficiency virus (HIV) and the pathogenic activity of most lentiviruses in the infected host, it is reasonable to assume that BIV should cause disease in cattle (10). BIV seropositivity has been associated with decreased milk production in dairy cattle, but has not been directly linked to clinical disease in naturally infected cattle (4-7,10,11). However, Walder et al. (12) reported evidence for a possible association between bovine paraplegic syndrome and a viral agent related to BIV. Snider et al. (13) determined that a herd with high seroprevalence of BIV had a high percentage of cows with encephalitis associated with depression and stupor, alteration of the immune system associated with secondary bacterial infections, and chronic inflammation of the feet and legs. In some cases, BIV-infected animals could be co-infected with bovine leukaemia virus (BLV), which can cause lymphoid tumours in the host, which commonly remains clinically and haematologically normal (7,14-18).

Experimental (19-22) and clinical evidence (10,18) showed that immune suppressive effects of BIV might be related to functional impairment of lymphocytes. Some authors (10,18) reported that no significant differences were found in total leukocyte populations or leukocyte subpopulations between BIV seropositive or seronegative animals; however, others (7,14,15,18) reported that BIV per se and a dual infection with BLV caused persistent lymphocytosis in cows. Circulating neutrophils and eosinophils were also reported to increase in BIV-inoculated sheep (23). Based on the accumulated evidence, it is difficult to decide whether BIV induces specific clinical and/or haematological syndromes in the host. Thus, this study was performed to evaluate whether routine clinical and haematological findings vary in BIV-infected dairy cattle in comparison to those in healthy controls. Clinical manifestations shown in cows in examined herds were recorded over 6 months in order to start a discussion on the incidence of clinical problems between BIV infected and non-infected cows. Recent advances in automated blood cell analysers have made it possible to give further information about complete blood cell count. Unfortunately, limited research has been reported on erythrocyte and platelet indices in cattle practice (24), and it is unknown yet whether these indices change in response to BIV infection. However, anaemia and thrombocytopaenia are often reported in patients with HIV (25,26). Therefore, erythrocyte and platelet indices were examined at the same time intervals in this study as well.

Materials and Methods

Animals

A total of 300 blood samples from cattle of Holstein (n = 294) and Simmental breeds (n = 6), in 4 different cities: Balıkesir, Bursa, Çanakkale, and Tekirdağ (Table 1), in the Marmara region (Turkey), were screened for anti-BIV antibodies (16). For this purpose, serum was separated by centrifugation at 3000 rpm for 10 min, heat inactivated and stored at -20 °C until sent to the Laboratory of Infectious Diseases, Hokkaido Univ., Japan by absorption on filter paper. BIV infection status of the cattle had been determined by Western blotting. Selected seropositive animals (n = 37; 12.3%) were further

Table 1. Detection of anti-BIV antibodies in cattle in Turkey.*

City	Number of cattle tested**	Number of cattle seropositive for BIV (%)
Balıkesir	50	6 (12.0)
Tekirdağ	41	4 (9.7)
Bursa	151	20 (13.2)
Çanakkale	58	7 (12.0)
Total	300	37 (12.3)

* Data summarised from Ref. 16

** The tested cattle were older than 1 year, and all were Holstein breed, except 6 of Simmental breed in Çanakkale.

sampled for confirmation of BIV infection by proviral DNA detection in buffy coat samples using nested polymerase chain reaction (PCR). BIV infected animals were monitored in the farm environment for the following 6 months for clinical and laboratory assessments. In this study, age matched BIV seropositive (test group, n = 37) and seronegative animals (control group, n = 37), of the same breed and lactation period, were used to assess any effect of BIV infection on clinical and haematological parameters. Control animals were selected from among BIV-seronegative cattle from the same herds including BIV-positive animals in 4 different cities. These cases were not further analysed for other infectious agents like viruses and bacteria that may play a role in that kind of clinical disorder. All the animals studied here were clinically normal at the first sampling time. Average age was 5.5 years in the test group and 4.6 years in the control group.

Measurements

Routine clinical and haematological parameters were obtained from test and control animals. Records were collected 6 times during visits once a month. Body temperature and heart and respiratory rates were recorded and external lymph nodes were examined by palpation. Peripheral (jugular) blood samples were collected from both groups and used to establish leukogram [total white blood cells (WBCs) and differential leukocyte counts], erythrogram [red blood cells (RBCs), haemoglobin (Hgb), haematocrit (Hct), and RBC indices: mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), and RBC distribution width (RDW)], and thrombogram [platelet count and platelet indices: mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW)], by use of an automatic haematology analyser (Cell Dyne 3500, Abbott, Wiesbaden, Germany).

Statistical analysis

All data were evaluated by one way analysis of variance (ANOVA) followed by Tukey test for pairwise comparisons (SigmaStat 2.0, GmbH, Germany). Clinical and haematological data in BIV-seropositive and BIV-seronegative groups were also compared using Student's t-test. P values less than 0.05 were considered significant. Results were expressed as mean ± SEM.

Results

Historical information from BIV-infected cattle revealed that the predominant diseases diagnosed during the observation period were mastitis (n = 18), metritis (n = 9), and respiratory system diseases (n = 8) (Table 2). At the same time, in the control group, mastitis (n = 1) and metabolic disturbance (n = 1) were diagnosed. During the monitoring period, there were no significant differences in temperatures between BIV-infected and control animals (Table 3). Heart and respiratory rates observed at 2-6 months were significantly higher ($P < 0.01$) in BIV-infected cattle than in control animals.

Of the haematological parameters, total WBC counts between $4.2 \pm 0.7 \times 10^3$/µl and $5.8 \pm 1.1 \times 10^3$/µl at 2-4 months were significantly lower ($P < 0.01$) in BIV-infected cattle, compared to those ($6.4 \pm 1.0 \times 10^3$/µl to $9.1 \pm 2.2 \times 10^3$/µl) in the controls. Neutrophil leukocytes ranging from 63 ± 10% to 88 ± 11% in BIV-infected animals were significantly higher ($P < 0.05$) than those (35 ± 9%-41 ± 5%) of control animals during the observation period. Lymphocyte rates were lower between 1 and 6 months in BIV-infected animals than in the controls (Table 4). Eosinophils, monocytes, and basophils rates did not vary within or between the groups (Table 4). RBC count ranged from 5.4×10^6/µl to 5.8×10^6/µl and 5.5×10^6/µl to 6.3×10^6/µl in test and control animals, throughout the study, respectively (Table 5). Haematocrit, haemoglobin, and RBC indices (MCV, MCH, MCHC, and RDW) varied insignificantly during the study in both groups. As shown in Table 6, variations in platelet count and platelet indices (MPV, PCT, and PDW) were not statistically significant between or within groups from the first sampling time to the end of the monitoring period.

Table 2. Clinical problems observed in 37 BIV-infected cattle.

Clinical problems	n (%)
Mastitis	18 (48.6)
Metritis	9 (24.3)
Respiratory system diseases	8 (21.6)
Retained placenta	7 (18.9)
Regional lymphadenopathy	7 (18.9)
Metabolic disturbance	6 (16.2)
Abomasal ulcer	2 (5.4)
Abomasal depletion	1 (2.7)

Table 3. Selected clinical parameters in healthy controls (n = 37) and BIV infected cattle (n = 37).

Parameters	Groups	Months (Mean ± SEM)						P
		1	2	3	4	5	6	
Temperature °C	Control	38.4 ± 0.5	38.3 ± 0.3	38.1 ± 0.8	38.6 ± 0.6	38.4 ± 0.4	38.3 ± 0.8	NS
	Infected	38.7 ± 1.2	38.2 ± 0.8	38.1 ± 0.9	38.8 ± 0.8	38.3 ± 0.9	38.0 ± 0.7	NS
Heart rate/min	Control	72.3 ± 7.6	68.7 ± 5.4	78.4 ± 3.2	82.3 ± 4.0	66.7 ± 4.4	76.4 ± 3.1	NS
	Infected	84.2 ± 2.8	94.3 ± 2.2†	68.4 ± 3.6	84.1 ± 6.8	78.3 ± 4.2†	88.4 ± 4.9†	NS
Respiration/min	Control	12.1 ± 4.2	14.2 ± 3.1	16.1 ± 3.0	13.0 ± 3.2	15.3 ± 4.3	16.2 ± 3.0	NS
	Infected	16.1 ± 6.4	20.2 ± 5.3†	14.4 ± 4.1	26.6 ± 5.2*†	24.2 ± 4.1†	27.5 ± 5.4*†	NS

NS: not significant

† Significant differences ($P < 0.01$) between control and BIV-infected groups.

* $P < 0.05$ versus value observed at 1st month

Table 4. White blood cell (WBC) and differential count in healthy controls (n = 37) and BIV-infected cattle (n = 37).

Parameters	Groups	Months (Mean ± SEM)						P
		1	2	3	4	5	6	
WBC count × 10^3/µL	Control	8.4 ± 1.5	6.4 ± 1.0	8.9 ± 2.6	9.1 ± 2.2	8.4 ± 1.3	7.5 ± 1.9	NS
	Infected	4.4 ± 0.8†	4.2 ± 0.7†	4.6 ± 1.2†	4.3 ± 2.4†	5.5 ± 3.4	5.8 ± 1.1	<0.05
Segment	Control	35.2 ± 9.4	38.3 ± 8.4	38.1 ± 6.3	41.2 ± 5.3	34.5 ± 6.7	36.3 ± 7.4	NS
Neutrophil %	Infected	68.4 ± 6.8†	63.1 ± 10.3†	78.7 ± 6.7†	69.5 ± 12.4†	88.2 ± 11.3*†	65.4 ± 9.3†	<0.05
Lymphocyte %	Control	55 ± 10	54 ± 9	52 ± 7	56 ± 9	61 ± 6	59 ± 7	NS
	Infected	27 ± 6†	34 ± 7†	29 ± 6†	27 ± 5†	10 ± 4**†	30 ± 5†	<0.01
Eosinophils %	Control	4 ± 2	4 ± 1	6 ± 2	2 ± 2	3 ± 2	2 ± 0	NS
	Infected	1 ± 1	2 ± 0	1 ± 1	1 ± 0	1 ± 1	3 ± 2	NS
Monocytes %	Control	5 ± 2	3 ± 2	3 ± 2	1 ± 0	2 ± 1	2 ± 1	NS
	Infected	3 ± 1	1 ± 1†	2 ± 1	2 ± 0	1 ± 1	2 ± 1	NS
Basophils %	Control	1 ± 0	1 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	NS
	Infected	1 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	NS

NS: Not significant

† $P < 0.01$; significant differences between control and BIV-infected groups

* $P < 0.05$ and ** $P < 0.01$; versus values observed at 1st visit

Table 5. Red blood cell (RBC) count and RBC indices in healthy controls (n = 37) and BIV-infected cattle (n = 37).

Parameters	Groups	Months (Mean ± SEM)						P value
		1	2	3	4	5	6	
RBC count × 10^3/µL	Control	6.1 ± 1.6	6.3 ± 1.3	5.5 ± 1.2	5.8 ± 1.1	6.0 ± 1.2	5.9 ± 1.4	NS
	Infected	5.6 ± 0.9	5.7 ±1.4	5.8 ± 1.0	5.6 ± 1.4	5.4 ± 1.1	5.5 ± 1.0	NS
Haematocrit %	Control	34 ± 3	36 ± 4	32 ± 2	29 ± 3	33 ± 4	32 ± 3	NS
	Infected	31 ± 4	34 ± 2	33 ± 3	32 ± 3	33 ± 2	33 ± 2	NS
Haemoglobin g/dl	Control	11 ± 2	12 ± 3	9 ± 2	9 ± 3	10 ± 2	9 ± 3	NS
	Infected	10 ± 3	11 ± 2	10 ± 3	9 ± 3	10 ± 4	11 ± 2	NS
MCV fl	Control	56 ± 5	57 ± 3	58 ± 4	50 ± 5	55 ± 3	59 ± 7	NS
	Infected	55 ± 4	59 ± 3	56 ± 2	57 ± 4	60 ± 4	60 ± 5	NS
MCH g/dl	Control	18 ± 3	19 ± 2	16 ± 4	16 ± 3	16 ± 4	16 ± 3	NS
	Infected	17 ± 4	19 ± 3	17 ± 5	17 ± 5	18 ± 5	19 ± 4	NS
MCHC pg	Control	32 ± 4	33 ± 4	29 ± 3	31 ± 4	30 ± 3	29 ± 4	NS
	Infected	32 ± 5	32 ± 5	30 ± 4	29 ± 3	31 ± 4	32 ± 3	NS
RDW %	Control	18 ± 3	16 ± 4	20 ± 3	19 ± 3	18 ± 4	17 ± 4	NS
	Infected	16 ± 4	17 ± 3	18 ± 4	17 ± 5	18 ± 3	18 ± 5	NS

MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin;
MCHC: Mean corpuscular haemoglobin concentration; RDW: RBC distribution width
NS: Not significant

Table 6. Platelet count and indices in healthy controls (n = 37) and BIV-infected cattle (n = 37).

Parameters	Groups	Months (Mean ± SEM)						P value
		1	2	3	4	5	6	
Platelet count	Control	320 ± 30	360 ± 80	340 ± 70	310 ± 90	330 ± 60	350 ± 70	NS
× 10^3/µL	Infected	360 ± 40	300 ± 60	290 ± 50	270 ± 40	320 ± 70	300 ± 80	NS
MPV fl	Control	15 ± 3	12 ± 4	15 ± 3	16 ± 2	17 ± 3	16 ± 3	NS
	Infected	18 ± 4	16 ± 3	17 ± 4	17 ± 3	15 ± 2	17 ± 3	NS
PCT %	Control	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.0	0.5 ± 0.0	0.6 ± 0.1	NS
	Infected	0.6 ± 0.1	0.5 ± 0.0	0.5 ± 0.0	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	NS
PDW %	Control	17 ± 2	18 ± 3	19 ± 3	18 ± 4	17 ± 3	19 ± 2	NS
	Infected	14 ± 3	15 ± 4	16 ± 3	17 ± 4	15 ± 2	16 ± 4	NS

MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet volume distribution width
NS: Not significant

Discussion

Seroepidemiological studies of BIV infections in cattle have been reported in many countries (1-7,9,13), including Turkey (16). Despite the worldwide distribution of BIV infection, whether the presence of BIV in a host leads to primarily pathologic changes or can cause secondary bacterial and/or viral infections as a predisposition factor has not been fully elucidated. Under practical conditions, infection with BIV has a different effect on the host than has been observed under experimental conditions (17). The presence of BIV combined with the stresses associated with parturition and a modern dairy production system was considered causal for the development of secondary diseases in immunocompromised cattle (8,17). In this study, during a 6-month observation period, the frequent development of concurrent infections in BIV-infected animals (Table 2) suggested that persistent BIV infection had a role in reducing functional immune competence, in accordance with other studies (17-19). In a previous study (17), the secondary disease processes and their incidence, including metritis (12%), subcutaneous abscesses (18%), purulent arthritis (18%), infectious pododermatitis and laminitis (37%), and mastitis (56%), were reported. It is interesting to note, like previously reported (17), that in the present study mastitis was the most common problem during BIV infection, most probably due to BIV induced immune dysfunction with a decreased CD4/CD8 ratio (17-19) and its transmission by milk (6,8). In the same study (17), clinical signs such as weight loss, reduced vitality, torpidity, dullness, and stupor in response to BIV were also reported. Metabolic disturbances (16%) observed in the study may be related to the clinical neurogenic anorexia observed in BIV-infected calves (17).

Regional lymphadenopathy in response to BIV has been reported in natural and experimental conditions (17). In the present study, the lymphadenopathy observed, probably due to an increased lymphocyte proliferation to BIV gag protein (19), may be interpreted as a useful diagnostic finding indicating the presence of BIV infection. Increased lymphocytic blastogenic activity in response to BIV (27) may also be a possible reason for the lymphadenopathy observed in this study. However, Snider et al. (17) reported that the enlarged lymph nodes in response to BIV did not represent the presence of lymphosarcoma. Hidalgo and Bonilla (20) reported that, due to the high rate of dual infections observed in Costa Rica, leukocytosis and lymphocytosis were not sufficient to clarify which virus is responsible for the suppressive activity, if one or both viruses are necessary, or if they act synergistically. During the monitoring period, there were no significant differences in body temperatures between BIV-infected and control animals (Table 3). Heart and respiratory rates observed at 2-6 months were significantly higher ($P < 0.01$) in BIV-infected cattle than in control animals, suggesting that these differences are most probably due to the clinical problems observed.

Studies showed that the BIV infection delayed antibody responses and decreased antibody titres to bovine herpesvirus type 1 (19) and bovine respiratory syncytial virus infection in cattle (27). Some studies (19,28) suggested that BIV may have a role as a predisposing factor for other viral diseases. Based on the our study design, it is difficult to decide whether the changes in circulating WBC counts and neutrophils rates were due to primarily BIV infection or secondary bacterial/other viral diseases. In contrast, some authors (10,17,18) reported that no significant differences were found in WBC populations and subpopulations between BIV seropositive or seronegative animals. Our observation that circulating lymphocytes were lower in BIV-infected cattle than in control animals was in contrast to a previous report (17) including lymphocytosis in 6 of 15 cows with BIV. In addition, Jacobs et al. (23) reported that neutrophil and eosinophil rates increased 3 months after BIV inoculation in sheep. Taken together, these conflicting data indicate that the role of BIV in the pathophysiological mechanism of bovine clinical diseases remains unclear.

It is well known that immunodeficiency viruses can cause bone marrow suppression, resulting in thrombocytopaenia and anaemia (25,26). Erythrocyte and platelet indices provide clinical information on the underlying conditions of anaemia and thrombocytopaenia (29). In particular, erythrocyte mean corpuscular volume (MCV) and mean platelet volume (MPV) have been reported to be indirect signs of disturbance of erythrocyte and platelet production and bone marrow response to infections (29). In the present study, erythrocyte and platelet indices did not differ within or between the groups, suggesting that BIV has no influence on the number, volume (MCV and MPV), or distribution width (RBC and PDW) in erythrocyte or platelets. This

observation may be related to the lower pathogenicity of BIV and duration of disease and infection, as reported earlier (1-7,9).

This study has some limitations. First, it is difficult to know whether the clinical and haematological disorders observed were due to BIV infection alone, because of the fact that BIV-positive cattle were not further analysed for other infectious agents like viruses or bacteria that may play a role in that kind of clinical disorder. Second, it is difficult to select uniform patient and control populations in animal studies. Therefore, control animals were selected from among BIV-seronegative cattle from the same herds including BIV-positive animals, because of the fact that some factors, i.e. climate, magnitude of farm, and management, are well known to affect the health status of dairy cattle. Thirdly, the number of lactations could have been recorded in the present study. The fact that there was no significant difference in age between the groups (5.5 years vs. 4.6 years) may have minimised the effects of lactation on clinical and haematological differences between them. Cavirani et al. (10) reported that clinical consequences of BIV infection might best be detected in older animals as well.

These findings suggest that the presence of BIV infections should be considered a health risk for cattle populations, and may have a role in the changes in WBC and differential cell counts in the host. Erythrocyte and platelet indices might be unchanged for 6 months in BIV-infected cattle. Further studies in a larger patient population are required to verify these observations.

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