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INVESTIGATION ON BIOCHEMICAL PARAMETERS OF CEREBROSPINAL FLUID IN CAMELS WITH NEUROLOGICAL DISORDERS

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ABSTRACT

This study was aimed to determine and compare CSF biochemical parameters in 8 healthy camels and 15 camels with neurological signs. The important neurological signs observed were shivering, tremour, staggering, rotation of the head, slight vision impairment and progressive worsening of general condition. Serum and CSF were collected for the biochemical analysis of the parameters. The results revealed that there was an increase in ALB, AST, TP, MG, NA, and TBIL values in the CSF obtained from camels showing neurological sings as compared to healthy camels.

Key words: Biochemical, camel, CSF, neurological signs, serum

Cerebrospinal fluid CSF) normally surrounds the brain and spinal cord and protects these from injury and nourishes and support central nervous system (Scott, 2010; Simon and Iliff, 2016). However, CSF is considered as a source of nutrition for the parenchyma of the brain and spinal cord (Achard *et al,* 2017). The normal chemical values of CSF in different animal species has been documented, i.e. horses, sheep, cattle, cats, dogs and various laboratory animals (Abate *et al,* 1998; Ahmed *et al,* 2009a; Ameri and Mousavian, 2007; Di Terlizzi and Platt, 2006; Nazifi and Maleki, 1998b; Stocker *et al,* 2002; Stokol *et al,* 2009; Welles *et al,* 1992b). Shawaf *et al* (2018) recently reported values for CSF constituents from healthy camels in Saudi Arabia.

The comparison of CSF analysis to serum has been used for diagnostic investigation of systemic abnormalities (Benedicenti *et al,* 2018; Stokol *et al,* 2009). However, the composition of CSF is strongly dependent on blood plasma constituents. Alterations in cerebrospinal fluid could be due to physiological and environmental conditions and diverse neurological diseases (Achard *et al,* 2017; Stokol *et al,* 2009).

Cerebrospinal fluid examination is done for inflammatory, neoplastic, traumatic, infectious, or degenerative disorders of the nervous system (NS) (Windsor *et al,* 2008), however, CSF analysis can rarely deliver a definitive diagnosis (Di Terlizzi and Platt, 2009).

Chemical analysis of CSF can provide evidence and information about the metabolism of the brain. It can also aid in the evaluation of CNS disruption, and it aids in biomarkers identification for the diagnosis of CNS diseases (Johanson *et al,* 2008). Cellular and chemical analysis of cerebrospinal fluid in different animal species have been used to monitor neurological disorders (Kumar and Kumar, 2012; Lampe *et al,* 2020; Simon and Iliff, 2016; Stokol *et al,* 2009). The cellular and biochemical parameters of cerebrospinal fluid helps in the evaluation of nervous system health status of living animals (AI-Sagair *et al,* 2005; Bellino *et al,* 2015; Frosini *et al,* 2000; Welles *et al,* 1992a).

Neurological signs observed in camels can be classified as infectious or noninfectious (Babelhadj *et al,* 2018; Shoeib *et al,* 2019). The infectious causes include viral, bacterial and prions diseases while the non-infectious causes are nutritional disorders. The neurological signs in camels manifest behavioural and neurological changes, i.e. meningitis, encephalitis, rhomboencephlistis, meningoencephalitis, stillbirth and abortion El Dobab *et al* (2008). Babelhadj *et al* (2018) studied neurological signs in camels and found severe spongiform degenerative changes in the brain tissues along with disease-specific prion protein.

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The main objective of this study was to determine and compare CSF biochemical parameters in healthy camels, and in camels with neurological signs.

Materials and Methods

Animals and sampling

Fifteen dromedary camels (age 2-21 years) with a history of neurological symptoms presented to the Veterinary Teaching Hospital, King Faisal University were investigated in this study. The main neurological symptoms observed in these animals were shivering, tremour, staggering, rotation of the head, slight vision impairment and progressive worsening general condition. Eight apparently healthy camels were used for comparison. Clinical examination was performed on all the subjected animals, venous blood samples were collected from the jugular vein. Animals were sedated and cerebrospinal fluid samples were collected aseptically from the Atlanto-occipital articulation as described by Shawaf *et al* (2018).

Biochemical samples analysis

Cerebrospinal fluid and serum samples were processed using Vet scan vs 2 analyser (ABAXIS, USA) to determine the concentration of albumin (ALB), gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alkaline phosphatase, total serum protein (TP), creatine kinase (CK), blood urea nitrogen (BUN), inorganic phosphorus (PHOS), potassium (K), magnesium (Mg), chloride (Cl), Sodium (Na), calcium (Ca), amylase, alanine aminotransferase, total bilirubin (TBIL), glucose (GLU) and creatinine (CRE).

Statistical analysis

Data was recorded in Excel spreadsheets and imported into Graph Pad Prism 7 software for further analyses. The data was analysed to determine the range, mean and standard error of the mean. To determine the significance, the student's t-test was used with a significance factor of $P < 0.05$.

Results

Table 1 shows the mean±SEM values of the chemical parameter's in the serum of clinically healthy dromedary camels (n=8) and camels with neurological disorders (n=15). The obtained results showed a significant increase in the serum parameters, i.e. ALB, AST, CK, Na, ALT, and TBIL in the affected camels, while a significant decrease in ALP, PHOS, Mg, K, and AMY were observed. No significant difference was observed in the following serum parameters of the affected and healthy camels, i.e. GGT, TP, BUN, Ca, Cl, CRE and Glucose.

Table 2 showed the mean±SEM values of the chemical parameters in the serum and CSF in camels with neurological disorders (n=15). Most parameters showed significant decrease in the CSF in comparison to values in serum. Only the chloride value was increased significantly in CSF compared to its value in serum of affected animals. No significant changes were observed in Mg, Na and K values among serum and CSF in affected animals.

The mean±SEM of CSF chemical parameters (Table 3) revealed that there was a significant increase in ALB, AST, TP, Mg, NA, and TBIL values in the CSF of affected animals. There was a significant decrease in CSF-Glucose in affected camels compared to healthy camels. However, there were no significant differences in ALP, GGT, CK, ALT, PHOS, Ca, Cl, K, ALT, BUN, AMY and CRE values.

Discussion

CSF chemical parameters compared to serum parameters are frequently used for diagnostic purposes, and to explain the nature of the disease process in CNS diseases and its severity (Kulkarni *et al,* 2009; Shawaf *et al,* 2018). Clinically, it was difficult to determine the main cause of neurological disorders in camels because these symptoms could be manifested by various other diseases (El Dobab *et al,* 2008).

In the present study, the concentrations of most biochemical parameters of the CSF for the camels with neurological symptoms were decreased compared to the levels in the serum. The same findings were reported in healthy camels (Nazifi and Maleki, 1998a; Saladin, 2012; Shawaf *et al,* 2018). This result may conclude that the values of biochemical parameters for camels are generally lesser in CSF vis-a-vis serum in both healthy and diseased animals, hence must be evaluated carefully for diagnostic purposes.

The results of this study revealed that AST levels were lesser in the CSF than serum which were in agreement with Ahmed *et al* (2009b) and Shawaf *et al* (2018) who also found similar results in camels. On the other hand, increased values of CSF-AST of affected camels as compared with healthy camels was in agreement with Tapiola *et al* (1998) in the case of Alzheimer's disease in humans. Increased AST in CSF for patients with meningitis was reported possibly due to outflow of enzymes from the destroyed cells

of CNS (Kulkarni *et al,* 2006). However, Thrall (2004) stated that the bigger molecules of AST, which can't pass through the blood brain barrier, leads to increased activities of this enzyme in the CSF, which could indicate damage of CNS cells. Moreover, Feldman (1997) and Indrieri *et al* (1980) stated a poor prognosis in affected animals with high AST levels in CSF. Normally, all the proteins which are found in the CSF are derived from plasma (Reiber *et al,* 2013), the levels are inversely related to its molecular weight (William Vernau *et al,* 2008). CSF protein levels are considered as one of the most sensitive indicators of a pathological process within the CNS (Kumar and Kumar, 2012). Similar results for the total protein in CSF of healthy camels were reported in healthy sheep (George, 1996). The total protein in CSF was in contrast with observations from a previous study in cattle (Welles *et al,* 1992a) and dogs (Hoerlein, 1978). Kumar and Kumar (2012) reported increased total protein in CSF in animals with viralor bacterial disease with was in agreement with the results of present study. According to Polizopoulou (2014) the increased concentrations of CSF total protein especially albumin can be attributed to the increased permeability of the blood-brain barrier. In contrast to our results, Bellino *et al* (2015) and Kumar (2012) reported less total protein concentration in CSF for affected cattle. However, Kumar and Kumar (2012) also reported decreased CSF protein in animals suffering from degenerative changes in CSN.

The main CSF protein is albumin which is produced only in the liver (William Vernau *et al,* 2008). Albumin synthesis only occurs extrathecally, while its increased level in CSF indicates damage to the CSF blood-brain barriers or CNS trauma. Barrier dysfunction can also be indicated by the ratio between CSF and serum albumin (William Vernau *et al,* 2008). A significant increase in CSF albumin was detected in the neurologically-manifested camels. Accordingly, this could indicate brain or meningeal diseases in the examined camels.

Creatinekinase (CK) consists of M and B subunits and may be traced in the brain, muscle, and heart (Ferreira *et al,* 2016). The results obtained indicated a highly significant elevation in the serum CK value for affected camels, compared to the CSF-CK value. This could be attributed to muscle damage during irregular movements, ataxia, or recumbency as a result of neurological disorders (Teodoro *et al,* 2019). The increased CK levels in CSF for affected animals compared to healthy animals was in agreement with Indrieri *et al* (1980); Jackson *et al* (1996); Kjekshus *et al* (1980) who observed a close correlation between the amount of brain injury and CSF-CK activity.

Table 1. Mean, SEM and range of biochemical value of blood serum in clinically normal dromedary camels (n=8) and camels with neurological disorders (n=15).

Parameter	Serum in healthy camels		Serum in affected camels		P value
	Mean ± SEM	Range	Mean±SEM	Range	
ALB (g/dl)	3.21 ± 0.24	2.4-4.0	5.28 ± 0.36**	4.1-6.7	0.009
ALP (IU/l)	183.8 ± 11.32	166-199	112.4 ± 13.96**	48-156	0.007
AST (IU/l)	143 ± 11.33	121-174	235.9 ± 93.01**	93-754	0.0095
GGT (IU/l)	14.45 ± 1.76	12.5-16.4	17.86 ± 5.02	10-47	0.25
TP (g/dl)	6.96 ± 0.33	6.43-7.23	7.17 ± 0.25	6.5-8.3	0.28
BUN (mg/dl)	14.2 ± 0.82	12.43-16.2	20.59 ± 2.37	12-47	0.14
CK (IU/l)	111.2 ± 25.7	95-145	277.1± 73.2***	168-714	0.008
PHOS (mmol/l)	5.98 ± 1.32	3.3-7.7	3.09 ± 0.28**	2.2-4.2	0.01
Mg (mmol/l)	2.83 ± 0.22	2.3-3.1	2.13 ± 0.15**	1.9-2.2	0.008
Ca (mmol/l)	9.68 ± 0.33	9.2-10.5	10.1 ± 0.34	8.9-11.2	0.35
Na (mmol/l)	151.1 ± 1.60	148-154	158.9 ± 2.37*	148-166	0.03
Cl (mmol/l)	113.5 ± 1.68	111-120	118 ± 1.31	114-122	0.1
K (mmol/l)	5.8 ± 0.56	4.8-6.2	4.66 ± 0.18*	418-5.5	0.02
ALT (IU/l)	14.11 ± 1.29	12-15	18.14 ± 1.33*	14-25	0.017
AMY (IU/l)	488.3 ± 21.8	461-533	270.9 ± 42.2**	105-450	0.003
TBIL (µmol/l)	0.2 ± 0.03	0.1-0.3	0.46 ± 0.14*	0.1-1.3	0.05
CRE (mg/dl)	1.39 ± 0.18	1-1.75	1.27 ± 0.12	0.8-1.8	0.28
GLU (mg/dl)	101.8 ± 15.61	71-143	97.7 ± 19.19	64-119.4	0. 1

Table 2. Mean, SEM and range of biochemical values of serum and CSF in affected dromedary camels with neurological disorders (n=15).

Parameter	Serum in affected camels		CSF affected camels		P Value
	Mean ± SEM	Range	Mean ± SEM	Range	
ALB (g/dl)	5.28 ± 0.36	4.1-6.7	0.77 ± 0.09***	0.41-1.02	0.0009
ALP (IU/l)	112.4 ± 13.96	48-156	53.43 ± 1.72**	48.2-59.3	0.008
AST (IU/l)	235.9 ± 93.01	93-754	33.14 ± 2.24***	25.8-41.35	0.0008
GGT (IU/l)	17.86 ± 5.02	10-47	4.54 ± 0.53***	4.12-9.98	0.00075
TP (g/dl)	7.17 ± 0.25	6.5-8.3	1.06 ± 0.18***	0.82-1.52	0.00033
BUN (mg/dl)	20.59 ± 2.37	12-47	9.33 ± 1.32**	9.90-10.90	0.006
CK (IU/l)	277.1± 73.2	168-714	30.14 ± 3.01***	21.3-39.8	0.0008
PHOS (mmol/l)	3.09 ± 0.28	2.2-4.2	0.51 ± 0.08***	0.20-0.89	0.0009
Mg (mmol/l)	2.13 ± 0.15	1.9-2.2	2.63 ± 0.11	2.1-2.92	0.38
Ca (mmol/l)	10.1 ± 0.34	8.9-11.2	5.14 ± 0.31**	3.48-6.01	0.008
Na (mmol/l)	158.9 ± 2.37	148-166	161 ± 3.18	144-171	0.19
Cl (mmol/l)	118 ± 1.31	114-122	136 ± 1.18*	127-140	0.045
K+ (mmol/l)	4.66 ± 0.18	418-5.5	4.52 ± 0.14	3.92-4.88	0.21
ALT (IU/l)	18.14 ± 1.33	14-25	10.57 ± 0.53**	8.2-12.12	0.007
AMY (IU/l)	270.9 ± 42.2	105-450	11.43 ± 0.78***	10.65-14.47	0.0006
TBIL (µmol/l)	0.46 ± 0.14	0.1-1.3	0.24 ± 0.04*	0.11-0.42	0.018
CRE (mg/dl)	1.27 ± 0.12	0.8-1.8	0.57 ± 0.06**	0.38-0.83	0.0035
GLU (mg/dl)	97.7 ± 19.19	64-119.4	72.3 ± 10.4*	59-83.6	0.031

Table 3. Mean, SEM and range of biochemical values of CSF in healthy (n=8) and affected dromedary camels with neurological disorders (n=15).

Parameter	CSF in healthy camels		CSF in affected camels		P Value
	Mean± SEM	Range	Mean± SEM	Range	
ALB (g/dl)	0.15 ± 0.03	0.1-0.19	0.77 ± 0.09**	0.41-1.02	0.0014
ALP (IU/l)	51.07 ± 1.4	48-55	53.43 ± 1.72	48.2-59.3	0.36
AST (IU/l)	25.24 ± 2.82	22-30	33.14 ± 2.24*	25.8-41.35	0.026
GGT (IU/l)	5.3 ± 2.35	3-8.2	4.54 ± 0.53	4.12-9.98	0.21
TP (g/dl)	0.71 ± 0.04	0.62-0.86	1.06 ± 0.18*	0.82-1.52	0.018
BUN (mg/dl)	8.98 ± 0.75	8.8-12.9	9.33 ± 1.32	9.90-10.90	0.26
CK (IU/l)	24.85 ± 3.39	17-30	30.14 ± 3.01	21.3-39.8	0.08
PHOS (mmol/l)	0.64 ± 0.08	0.5-0.91	0.51 ± 0.08	0.20-0.89	0.095
Mg (mmol/l)	2.11 ± 0.07	2-2.3	2.63 ± 0.11*	2.1-2.92	0.018
Ca (mmol/l)	4.77 ± 0.08	4.6-5.0	5.14 ± 0.31	3.48-6.01	0.17
Na (mmol/l)	153.5 ± 0.82	151-156	161 ± 3.18*	144-171	0.019
Cl (mmol/l)	128.3 ± 2.2	123-133	136 ± 1.18	127-140	0.095
K+ (mmol/l)	4.22 ± 0.04	4.2-4.33	4.52 ± 0.14	3.92-4.88	0.11
ALT (IU/l)	10.54 ± 0.43	10.1-11.8	10.57 ± 0.53	8.2-12.12	0.47
AMY (IU/l)	9.71 ± 1.23	8-15	11.43 ± 0.78	10.65-14.47	0.075
TBIL (µmol/l)	0.14 ± 0.02	0.1-0.2	0.24 ± 0.04*	0.11-0.42	0.028
CRE (mg/dl)	0.6 ± 0.06	0.5-0.7	0.57 ± 0.06	0.38-0.83	0.35
GLU (mg/dl)	90.8 ± 9.69	100.3-80.2	72.3 ± 10.4*	59-83.6	0.037

In the current study an increase in the concentrations of sodium values was found in both the serum and the CSF from affected camels. Kulkarni *et al* (2009) reported the similar results for sodium in CSF in poisoned cases. Our results agreed with Kumar and Kumar (2012), who reported that Na concentrations are similar in both CSF and serum.

The obtained results for Cl and Ca levels were in agreement with Kumar and Kumar (2012). Chloride levels were higher in the CSF than in the blood, while the calcium concentration was less in CSF for healthy and affected groups. Contrary to our results Tan *et al* (2014) reported decreased values of Cl in CSF patients with bacterial meningitis. According to Kumar and Kumar (2012), the increased concentrations of CSF-Ca indicates the presence of damage in the blood brain barrier.

Magnesium has an important role in the nervous system for ideal nerve transmission, calcium channel antagonism and neuromuscular coordination. It also helps to prevent excitotoxicity (Grober *et al,* 2015). The results for Mg in serum and CSF in affected camels were interesting. The Mg concentration decreased in serum from affected animals in comparison to its levels in serum from healthy animals, while there was an increase in CSF-Mg for affected animals compared to its levels in CSF of healthy animals. Our results for decreased magnesium in serum from affected camels were in agreement with earlier observations in camels affected with Dubduba Syndrome (Al-Mujalli *et al,* 2011). However, it is well known that insufficiency of Mg results in muscle cramps, increased irritability, weakness, tremors and jerking (Al-Mujalli *et al,* 2011). Similar to our results Reynolds *et al* (1984) reported increase in CSF-Mg and decrease in serum of calves affected with hypomagnesaemia. Similarly, results of increased CSF-Mg in people with epilepsy was reported (Alvarez-Domínguez *et al,* 1978; Ileana Benga *et al,* 1985). In contradiction to our results, Bayir *et al* (2009) reported lower CSF-Mg in people with brain injuries. The difference in Mg concentration among serum and CSF in affected animals could be attributed to the fact that there is no direct relation between Mg in serum and CSF, which confirms the theory that the infusion of Mg compounds into blood had no influence on CSF-Mg concentrations (Mercieri *et al,* 2012).

CSF glucose is transported through facilitated diffusion from the plasma, in which its levels in CSF are relying on glucose levels in the blood-CNS metabolic rate, and glucose amount delivered into the CSF (William Vernau *et al,* 2008). The ratio of CSF/serum glucose are ranged between 40-60% in healthy camels (Ahmed *et al,* 2009b; Shawaf *et al,* 2018). Decreased CSF-glucose in affected camels compared to healthy camels in the present study was in agreement with previous studies in humans with several disorders of the nervous system like meningitis (Roberts *et al,* 2014; Troendle and Pettigrew, 2019) and severe encephalomyelitis (Troy *et al,* 2008); and also with dogs with nervous distemper (Ettinger and Feldman, 2005). Additionally, a decreased glucose levels in CSF (hypoglycorrhachia) in animals is related with bacterial meningitis or systemic hypoglycemia (Bailey and Vernau, 1997; George, 1996), which agreed with the results of this study in camels that are affected by neurological disorders. The serum glucose of affected camels was decreased in the present study compared to the levels in serum of healthy camels, which could explain its lower levels in CSF in affected camels. However, Deisenhammer *et al* (2011) also reported that the elevated levels of CSF glucose had no significant diagnostic importance, as it proportionately increased with blood glucose in case of diabetes.

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