Journal of Basic and Clinical Veterinary Medicine

2021; 2(1): 32-37

Official Journal of Veterinary Faculty of Islamic Azad University
Urmia Branch

Journal Homepage: jbcvm.iaurmia.ac.ir

Evaluation of plasma changes of hepcidin, total sialic acid and sphingosine 1 phosphate in buffaloes with hepatic hydatidosis

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ARTICLE INFO

Received: 11 May 2021

Accepted: 10 December 2021

DOI:10.30495/jbcvm.2021.1930308.1008

KEYWORDS:

Hepcidin
Total sialic acid
Sphingosine 1 phosphate
Buffalo
Hydatidosis

ABSTRACT

The aim of this study was to evaluate plasma changes in hepcidin, total sialic acid (TSA) and sphingosine 1 phosphate (S1P) in buffalos with hydatidosis in the city of Urmia. Hydatidosis is a zoonotic disease that can be very dangerous in humans and even cause death to humans and animals. In this study, the samples were taken from 40 cases of buffalos that suffered from hydatidosis, especially the liver form of the disease, and also 40 buffaloes without hydatidosis all taken from Urmia slaughterhouse. After the separation of plasma samples, the mentioned parameters were measured and analyzed statistically using SPSS version 17. The results indicated a significant increase $P<0.05$ in all mentioned parameters compared to the healthy group. Based on the above result, it can be noted that hydatidosis causes changes in plasma levels of some parameters. Interpreting some of the parameters would help us come to a better understanding of the complications of the disease. Furthermore, focusing on these parameters along with other plasma parameters would help practitioners in the paraclinical diagnosis of buffalo's hydatidosis.

بررسی تغییرات پلاسمایی هپسیدین، توتال سیالیک اسید و اسفنگوزین ۱ فسفات در گاومیش های مبتلا به هیداتیدوزیس کبدی

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چکیده

این مطالعه با هدف بررسی تغییرات پلاسمایی هپسیدین، توتال سیالیک اسید و اسفنگوزین ۱ فسفات در گاومیش های مبتلا به هیداتیدوزیس کبدی در شهرستان ارومیه صورت گرفت. هیداتیدوزیس جزء بیماری های مشترک بین انسان و دام می باشد که می تواند در انسان بسیار خطرناک باشد و حتی خسارات جانی را برای انسان و حیوانات در پی داشته باشد. این بیماری در حیوانات با خسارات اقتصادی همراه بوده می تواند از لحاظ اقتصادی برای جامعه دامی کشور بسیار آسیب رسان باشد. در این مطالعه از ۴۰ نمونه گاومیش های کشتاری در کشتارگاه ارومیه که به فرم کبدی هیداتیدوزیس مبتلا بودند و به همان مقدار نمونه گاومیش های سالم، خونگیری انجام گردید و بعد از جداکردن نمونه های پلاسما، پارامترهای فوق الذکر مورد بررسی و ارزیابی آماری با استفاده از ویرایش ۱۷ SPSS قرار گرفت. نتایج نشانگر ارتباط معنی دار $P<۰/۰۵$ در کلیه پارامترهای مذکور به نسبت گروه شاهد می باشد. بر این اساس می توان گفت که بیماری هیداتیدوزیس می تواند باعث بروز تغییراتی در مقادیر پلاسمایی در برخی از پارامتر ها گشته و ممکن است بتوان با تفسیر برخی از پارامتر های ذکر شده کمک شایانی در شناخت هرچه بیشتر عوارض ناشی از بیماری داشته و همچنین می توان با بررسی های وسیعتر از پارامترهای یاد شده به همراه دیگر پارامترهای پلاسمایی در تشخیص بیوشیمیایی (بیومارکر) هیداتیدوزیس گاومیش نمود.

واژه های کلیدی: هپسیدین، توتال سیالیک اسید، اسفنگوزین ۱ فسفات، گاومیش، هیداتیدوزیس

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INTRODUCTION

Hydatidosis is zoonotic disease that can be very dangerous in human and even cause death to humans and animals. The problem of diseases transmitted between animals and humans has many aspects, especially as it is not uncommon for animals serving as reservoir or intermediate hosts to be clinically in apparent carriers and/or excreters of an agent [1.2.4]. Undoubtedly, currently unknown zoonoses will be discovered in future. New methods for direct or indirect detection of microorganisms contributing to the detection of new zoonoses will be presented [2.3].Parasitic zoonoses belong to the most important human diseases worldwide [1.5.6]. They are caused by protozoa [7.8.9], helminths [trematodes (flukes) [9.10], cestodes (tapeworms) [8.13] , and nematodes (round worm s)][11.15.19], Acanthocephala (thorny-headed worms) , pentastomids (tongue worms)[13.11], and arthropods. The last of these plays an additional role as a transmitter of viruses [14.15], rickettsiae, bacteria, protozoa, and helminths [13.14]. Cystic echinococcosis is a chronic disease caused by expansive growth of Echinococcus cysts (meta cestodes) [20]. The disease is caused by metacestodes(echinococcuscysticus) of the small dog tapeworm, E. granulosus.l. Several strains, differing in biology, host preferences, biochemistry, and genetics are known [20.21]. Carnivores play substantial effect as definitive hosts, while domestic ungulates and human are involved as the intermediate hosts. Similarly, sheep participate in disease transmission and the strain (G1) of Echinococcus granulosuscauses (cystic Echinococcus) [19.20.21]. It is usually asymptomatic in livestock, however, inspection of carcass at the slaughter house can lead to detection of disease [18.21].

The 25-amino acid peptide hepcidin plays a central role in iron homeostasis. Synthesized in the liver as an 84-amino acid precursor (prohepcidin), hepcidin binds to the cellular iron exporter, ferroportin, triggering its internalization and degradation. The consequent decrease in ferroportin produces a “mucosal block” by lowering iron absorption in the intestine and depresses recycling of the iron liberated by red blood cell turnover. Together, these result in a reduction in circulating iron levels (hypoferremia) as well as reduced placental iron transfer during pregnancy [49]. When plasma iron levels are high, hepatic synthesis of hepcidin increases, reducing both iron absorption and recycling. Liver cells monitor iron levels using a multicomponent “iron-sensing complex” comprised of two transmembrane receptors whose cores consist of homodimers of TfR1 and TfR2, respectively, linked by a third transmembrane protein, HFE protein. HFE protein is a major histocompatibility (MHC) class 1–like molecule that binds β2-microglobulin and, normally, TfR1 [32]. TfR1 also binds the iron-bound form of transferrin (Tf-Fe). The binding sites for Tf-Fe and HFE overlap. Consequently, when iron is abundant and Tf-Fe levels are high, HFE is displaced from TfR1. The displaced HFE protein then binds to TfR2, forming a complex that can be further stabilized by binding of Tf-Fe. Binding of HFE to TfR2 triggers an intracellular signaling cascade that activates expression of HAMP, the gene encoding hepcidin. The gene encoding HFE protein is commonly mutated in hereditary hemochromatosis [32.33].

The sialic acids are N- or O-acyl derivatives of neuraminic acid. Neuraminic acid is a nine-carbon sugar derived from monoamine (an epimer of glucosamine) and pyruvate. Sialic acids are constituents of both glycoproteins and gangliosides [28]. Glycoproteins (also

known as mucoproteins) are proteins containing branched or unbranched oligosaccharide chains, including fucose. They occur in cell membranes and many proteins are glycosylated. Sulfogalactosyl ceramide and other sulfolipids such as the sulfo (galacto)-glycerolipids and the steroid sulfates are formed after further reactions involving 3′-phosphoadenosine-5′-phosphosulfate (PAPS; "active sulfate") [29]. Gangliosides are synthesized from ceramide by the stepwise addition of activated sugars (eg, UDPGlc and UDPGal) and a sialic acid, usually N-acetylneuraminic acid [30]. A large number of gangliosides of increasing molecular weight may be formed. Most of the enzymes transferring sugars from nucleotide sugars (glycosyltransferases) are found in the Golgi apparatus [31].

Sphingolipids were discovered in the last years of the 1980's and named after the mysterious Sphinx because of their puzzling biological function [22.24]. It was not until the 1990s that sphingosine and its sphingoid derivatives became known as signaling molecules that mediated biological functions such as cell differentiation, migration, survival, and metabolism. Genetically modified studies in mice have described the existence of important physiological functions of S1P signaling in various human diseases including pulmonary arterial hypertension [28.24], diabetes, liver disease, and gastrointestinal diseases (GI) [25]. In addition, advances in drugs that affect the S1P signaling pathways make it possible to modulate vital cellular pathways, while also providing a way to treat various diseases. [27]. The growing epidemic of obesity in Western countries has attracted special attention to the liver and gastrointestinal tract (intestinal-liver axis) due to their physiological role in lipid metabolism and nutrient distribution [26]. Simultaneously, S1P signaling is a key factor in metabolic diseases, various liver injuries such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and liver fibrosis, and gastrointestinal diseases such as inflammatory bowel disease (IBD) appears and colorectal cancer [28].

Mindfully hydatidosis can be transmitted to humans and in some cases has caused the death of humans, so studying and recognizing it is of particular importance. There have been numerous medical and veterinary articles on epidemiology and parasitology in relation to hydatid cysts, but unfortunately no biochemical factors such as hepsidine, sphingosine monophosphate, and total cialic acid have been investigated in buffalo. It is hoped that the present study will be able to take a small step towards recognizing this important disease so that colleagues and researchers can more effectively control it in the future.

MATERIALS AND METHODS

In the present study, 40 blood samples from buffalos with severe hepatic hydatidosis (patient group) were macroscopically identified in the Urmia slaughterhouse (West Azerbaijan province), Iran. Ten milliliters of blood were collected via the jugular vein of buffalos that had been admitted for slaughtering at the abattoir of Urmia and blood samples transferred equally to EDTA-contained and non-EDTA contained tubes. After slaughtering, animals were surveyed based on observation of severe hepatic CE in liver. (40 blood samples) Buffalo without macroscopic lesions and no blood parasites in their blood were considered as healthy groups. It should be noted, however, that the blood sample was first transferred to tubes

containing appropriate amounts of EDTA anticoagulants and secondly, microscopic examination to determine the presence or absence of blood parasites using Giemsa staining (5% solution) was carried out. The blood samples were centrifuged at 6000 rpm for 10 min and their plasma was separated and frozen at 25 ° C until the test. The plasma S1P level was determined using a RA1000 in accordance with the ELISA method by (East Biopharm, Hangzhou, China). TSA was measured by Sydow method. Hepcidin was measured by ELISA method (Bioassay Technology Laboratory, China).

Statistical analysis was accomplished in all analyses. The Mean ± SD and the determination of variation between the data results were carried out with Student's t-test through SAS v9.1 (SAS Institute Inc., Cary, NC, USA). The significance level was specified at ($P<0.05$). Moreover, determination of cut-of point among with ROC analysis were carried out in all parameters for sensitivity and specificity detection.

RESULTS

The results of Kolmogorov-Smirnov test indicate that the significance level of the research parametersare less than the criterion coefficient of 0.05, so the research parameters have normal distribution and precondition of independent t-test. As the results of the independent t-test indicate, the significance level is less than the significance level of 0.05 in comparing the mean of the two groups of patients and healthy, so with 95% confidence we can say that there is a significant difference between the mean of healthy and patient groups. This means that the concentration of total sialic acid, hepcidin, sphingosine 1 phosphate (S1P) in the patient groups were significantly higher than in the healthy groups (Table1).

DISCUSSION

The results of this study showed a significant ($P <0.05$) increase in all plasma parameters in the patient group compared to the healthy group. Concerning total sialic acid, a study by Chrostek et al in 2011 showed that there was a significant decrease in LSA lipid-bound sialic acid in patients with non-alcoholic cirrhosis. Chrostek attributes the possible cause of a significant decrease in sialic acid to changes in hepatic sialyl transferase activity [36]. Another study by Stefanelli in 1985 showed a significant decrease in total sialic acid following cirrhosis [37]. In a study by Yurtseven in 2009, a significant decrease in sialic acid was observed in cattle infected with theileriosis, and even reported a possible cause of the slowdown in protein sialization and overall decrease in glycoprotein production in the liver38. It is worth noting that extensive studies have reported significant increases in sialic acid in various diseases such as heart disease, hyperglycemia and diabetes,

Table 1. Alterations of plasma S1P, Hepcidin and TSA levels in the control and patient groups

Parameters	Control Group	Patient Group
TSA (mg/dl)	11.52 ± 1.21	69.41 ± 3.01*
Hepcidin (pg/mL)	48.71 ± 5.25	356.13 ± 32.41*
S1P (ng/l)	224.69 ± 38.12	1289 ± 79.81*

The asterisk (*) indicates a significant difference in the patient group compared to the healthy group.

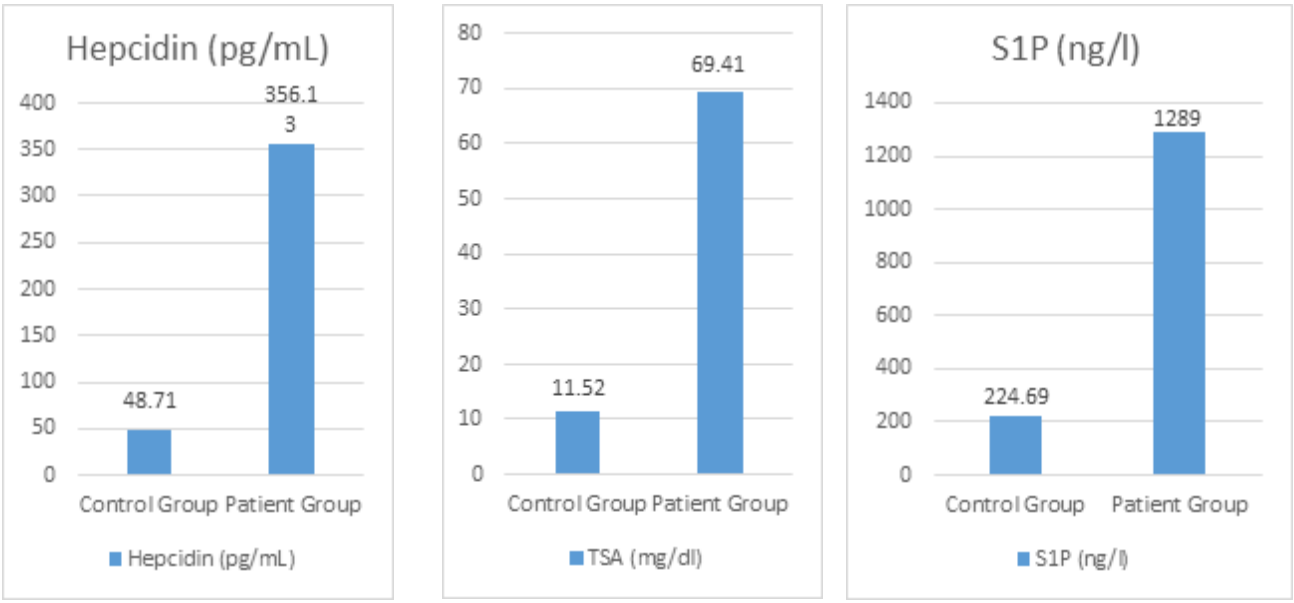

Figure 1. Alterations of plasma S1P, Hepcidin and TSA levels in the control and patient groups

malignancies and inflammatory disorders in humans and animals, and even sialic acid. They have been mentioned as one of the inflammatory markers in the diagnosis of some diseases.

Plasma total sialic acid may be significantly increased in buffaloes with hydatid cysts due to the stimulatory effect of the aforementioned disease on the synthesis and production of sialic acid following inflammation and disease because sialic acid is one of the inflammatory markers found in the acute phase of the disease increases [35]. In relation to hepcidin, elevated plasma hepcidin levels in diseased individuals have been recognized as a body defense mechanism to reduce the availability of pathogens to iron, and many studies have also shown that between elevated levels of 6-IL and 1-IL with increased Hepcidin levels there is a significant positive relationship [40] and, therefore, they consider hepcidin as an acute phase II protein. Many studies are currently underway to introduce hepcidin as a diagnostic marker for diseases [34.42]. Tan et al. (2012) attempted to use the ratio of hepcidin to ferritin as a diagnostic marker for the diagnosis of hepatic cirrhosis41. In another study, hepcidin was used as a biomarker to detect the severity of biliary inflammation [34.42]. Cherian et al. used hepcidin to diagnose and differentiate Helicobacter pylori infection from intestinal worm infection in children [46]. Wu et al. (2013) identified serum hepcidin as a biomarker for the diagnosis of sepsis in low birth weight infants [44]. Hepcidin levels are increased even in the absence of an acceptable acute phase response, and this feature makes it susceptible to be studied as a biomarker for disease detection [43.47]. The present study showed that the plasma levels of S1P in the patient group were significantly higher than the control group ($P < 0.05$). The remarkable impact of S1P on the function of monocytes as well as T and B lymphocytes has been demonstrated [39]. This molecule plays an important and fundamental role in the maturation and migration and tissue distribution of T and B lymphocytes and contributes to the activity of T cells [48]. Activation and stimulation of T and B lymphocytes by immune stimuli have been reported to decrease expression and subsequently decrease S1P synthesis. One of the biomolecules in plasma that contains S1P is high-density lipoprotein (HDL) [47]. This

molecule participates in the degradation and elimination of Trypanosoma's blood parasite and is likely to play an important role in increasing plasma S1P. There are no published papers on plasma changes of S1P in hydatid cysts. However, it is likely that hydatid cysts will directly increase S1P gene expression by unknown mechanisms.

ETHICS

All procedures of the current research have been performed based on the ethical standards.

CONFLICT OF INTEREST

None.

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