doi: 10.13241/j.cnki.pmb.2017.27.011

·临床研究·

哈夫病的单中心临床分析 *

刘 瑾 曹红娣 李 昂 江 蕾 何伟春 徐玲玲△

（南京医科大学第二附属医院肾脏病中心 江苏 南京 210003）

摘要 目的:探讨我院哈夫病的临床特点,旨在提高对本病的认识并提供一些诊疗体会。**方法:**回顾性分析 2016 年 7 月～8 月在我院肾病中心住院诊治的哈夫病患者,收集该人群的临床资料,并行统计学分析。**结果:**2016 年 7 月至 8 月我科累计收治哈夫病患者 66 例,其中男性 28 例(42.4%),女性 38 例(57.6%),发病年龄 35.5 岁(18-76 岁),潜伏期 5.6 小时(1-24 小时),患者发病前均有食用小龙虾史,首发症状均为肌肉酸痛,部分伴有浓茶色尿(19 例,28.8%);实验室检查提示转氨酶及肌酶升高明显(丙氨酸氨基转移酶、天冬氨酸氨基转移酶、乳酸脱氢酶、磷酸肌酸激酶、肌红蛋白,肌酸激酶同工酶),部分患者尿检异常,尿隐血阳性(45%)、尿蛋白阳性(16.7%)。经治疗后所有患者肌肉酸痛症状缓解,尿色转清,复查上述转氨酶及肌酶均明显下降(P<0.05),尿隐血及蛋白均转阴。**结论:**南京哈夫病夏季高发,与食用小龙虾有相关性,潜伏期短,首发症状多为肌肉酸痛,伴或不伴有肌红蛋白尿,实验室检查示血清磷酸肌酸激酶、肌红蛋白、肌酸激酶同工酶升高明显,疗程短,预后佳,一般不留后遗症。

关键词:哈夫病;横纹肌溶解;肌红蛋白

中图分类号:R595.7 **文献标识码:**A **文章编号:**1673-6273(2017)27-5247-04

Clinical Analyzation of Patients with Haff Disease in a Single Center*

LIU Jin, CAO Hong-di, LI Ang, JIANG Lei, HE Wei-chun, XU Ling-ling△

(Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, 210003, China)

ABSTRACT Objective: To explore the clinical characteristics of Haff disease in our hospital, be familiar with the disease and provide some experience in diagnosis and treatment. **Methods:** Inpatients with Haff disease in our Kidney disease center between July and August 2016 were retrospectively analyzed. The clinical data of patients was collected and statistically analyzed. **Results:** There were 66 patients (28 of male and 38 of female) in total with Haff disease between July and August 2016 in our ward. The average onset age was 35.5 years old (18-76 years old) and the average latency period was 5.6 hours (1-24 hours). All the patients had crayfish before the onset of the disease. The initial symptoms included muscle pain and concentrated brown urine (19 cases, 28.8%). Laboratory tests suggested that transaminase and myotropin were increased significantly (alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, myoglobin and creatine kinase isoenzyme). A trace of blood (45%) and protein (16.7%) was present in some patients' urine test. After treatment, muscle pain was alleviated and urine color turned to clear in all patients. All the transaminase and muscle enzymes were significantly decreased (P<0.05). No blood or protein was detected in the urine test. **Conclusions:** The epidemiology of Haff disease in summer at Nanjing was related to the intake of crayfish. The latency period was short and the initial symptoms were mostly muscle soreness, with or without myoglobinuria. Laboratory tests showed serum creatine phosphokinase, myoglobin, creatine kinase isoenzymes were increased significantly. The treatment period was short with good prognosis. Generally no sequelae was observed.

Key words: Haff disease; Rhabdomyolysis; Myoglobin

Chinese Library Classification(CLC): R595.7 Document code: A

Article ID: 1673-6273(2017)27-5247-04

前言

哈夫病为食用某些水产品 24 小时以内发生的横纹肌溶解征,1924 年国际上首次报道了该病例,因发生在波罗的海哈夫地区,而被称为哈夫病[1]。其典型临床表现为横纹肌溶解突然发作,伴有肌肉触痛、僵硬、酱油色尿等,发病与摄入水产品有关。其中淡水鱼类、小龙虾等均有致病记录[2-7],但致病机制不详,怀疑与一种尚不明确的耐热性毒素有关[3]。临床上大多散发,亦有小规模流行,主要发病季节为夏、秋季[8],发病地区包括美国、巴西和德国等[8-10],2000 年北京首次报道了因进食蝲蛄引起哈夫病的病例[11],此后其发病地区逐渐扩大,累及上海、深圳、香港等多个省市,多数仍仅限于个案报道[12-17],但在广东及江苏省曾

* 基金项目:国家自然科学基金青年科学基金项目(31300955);江苏省自然科学基金面上项目(BK20141489)

作者简介:刘瑾(1986-),女,硕士研究生,住院医师,主要研究方向:慢性肾脏病,电话:15850570476,E-mail:liu-jinliujin@163.com

△ 通讯作者:徐玲玲,女,硕士研究生,主治医师,讲师,主要研究方向:慢性肾脏病,电话:13815887273,E-mail:xulingling@njmu.edu.cn

(收稿日期:2017-04-14 接受日期:2017-05-10)

有爆发流行，主要因食用小龙虾发病[18-23]。小龙虾是一种淡水甲壳纲动物，近年来需求量日趋增多，南京每年 6~9 月日均消费 60-89 吨小龙虾。研究表明，食用小龙虾与哈夫病流行有密切相关[24]。本文分析了 2016 年我科收治的哈夫病患者的临床特征，旨在提高对本病的认识。

1 对象和方法

1.1 研究对象

2016 年 7~8 月在南京医科大学第二附属医院肾内科住院确诊为哈夫病患者共 66 例，均纳入本研究，收集患者的性别、发病年龄、病程、潜伏期、首发症状、蛋白尿、隐血、酱油尿的发生情况。其中男性 28 例，女性 38 例，发病年龄 18-76 岁(中位年龄 35.5 岁)。均符合以下条件[3]：(1)横纹肌溶解突然发作，伴随肌肉触痛、僵硬、酱油尿等；(2)24 小时内有食用淡水鱼类或甲壳类动物史；(3)排除其他因过量运动、缺血、代谢紊乱、药物、自身免疫等因素导致的横纹肌溶解征。

1.2 方法

采集患者发病及出院时的血、尿标本，检测血常规、丙氨酸氨基转移酶、天冬氨酸氨基转移酶、尿素氮、肌酐、乳酸脱氢酶、磷酸肌酸激酶、血清肌红蛋白、肌酸激酶同工酶、血清肌钙蛋白 T 以及尿常规等相关指标。

1.3 统计学分析

数据使用 SPSS13.0 统计软件，计数资料以均数± 标准差或中位数表示，组间比较采用 t 检验或非参数检验。P<0.05 为差异有统计学意义，P<0.01 为统计学差异显著。

2 结果

2.1 一般临床资料

66 例患者中男性 28 例(42.4%)、女性 38 例(57.6%)，男女比例 1:1.4，发病年龄 35.5 岁(18~76 岁)，潜伏期 5.5 小时(1~24 小时)。患者发病前均有食用小龙虾史，首发症状均为肌肉酸痛(包括颈部、躯干及四肢肌肉)，其中尿隐血阳性 30 例(45%)，仅 1 例尿沉渣红细胞计数 >10 万 /mL，19 例出现酱油色尿(28.8%)。

2.2 实验室指标

患者入院后查血白细胞、血红蛋白、超敏 C 反应蛋白未及明显异常，但天冬氨酸氨基转移酶 88.5IU/L(22~1554U/L)、乳酸脱氢酶 303IU/L (150~2342IU/L) 指标略偏高，磷酸肌酸激酶 3271IU/L(223~163200IU/L)、肌红蛋白 1121.5 ng/mL(29.9~35974 ng/mL)、肌酸激酶同工酶 78.1 ng/mL(3.7~1676 ng/mL)升高明显。所有患者血尿素氮、肌酐指标无明显异常(表 -1)。

表 1 患者的实验室检查(入院时)

Table 1 Laboratory tests of the study population(baseline)

	Test values(n=66)	Reference values
WBC(10^9/L)	9.5± 3.9	4.00-10.00
Hemoglobin(g/L)	137.7± 15.5	120.0-160.0
CRP(mg/L)	4.5(1-32)	0-10.0
Direct bilirubin(umol/L)	4.2± 1.6	0-5.1
Indirect bilirubin(umol/L)	6.8± 3.9	1.7-10.2
Albumin(g/L)	44.5± 3.8	39.7-49.4
ALT(IU/L)	47(13~316)	0-41
AST(IU/L)	88.5(22~1554)	0-40
CK(IU/L)	3271(223~163200)	39.0-308.0
LDH(IU/L)	303(150~2342)	135.0-225.0
Myoglobin(ng/mL)	1121.5(29.9~35974)	28.0-72.0
CK-MB(ng/ml)	78.1(3.7~1676)	0-4.9
Troponin T(ng/ml)	0.004(0.001~0.07)	0-0.014
Bun(mmol/L)	4.6± 1.4	1.7-8.3
Creatinne(umol/L)	63.5± 16.1	59.0-104.0

WBC: White blood cell count, CRP: C-reactive protein, ALT: Glutamic pyruvic transaminase, AST: Glutamic oxaloacetic transaminase, CK: Creatine phosphokinase, LDH: Lactate dehydrogenase, CK-MB: Creatine phosphokinase-MB, Bun: Usea nitrogen.

2.3 预后

患者平均住院日 6.6± 2.7 天(2-15 天)，经治疗后所有患者肌肉酸痛症状缓解，尿色转清，复查血清直接胆红素 4.2± 1.6 μmol/L、间接胆红素 6.8± 3.9 μmol/L、丙氨酸氨基转移酶 47 U/L、天冬氨酸氨基转移酶 88.5 U/L、磷酸肌酸激酶 3271 IU/L、肌红蛋白 1121.5 ng/mL、肌酸激酶同工酶 78.1 ng/mL，指标较入院时明显下降且存在统计学差异。(表 -2)。尿隐血及蛋白均转阴。

3 讨论

自 2009 年北京首次报道哈夫病以来，其发病地区逐渐扩大，但疫情主要发生在江苏省南京市[19-22,24-27]，2010 年南京市曾有爆发流行，发病人数达 42 人，食用小龙虾几乎是该病爆发流行的主要因素，且主要累及人群为成年人，好发于夏秋季[19-22]，表明饮食习惯及季节性分布是哈夫病流行的重要特征。本文研

究发现,2016 年 7~8 月期间仅我院收治哈夫病患者 66 例,发病人数明显较前增多, 平均发病年龄 36 岁, 均有食用小龙虾史,与既往文献报道一致。近年来,食用小龙虾者日趋增多,尤其是南京市民,每年 6~9 月为高发季节,尤其是近期有食用小龙虾史,出现不明原因横纹肌溶解的病例,在鉴别诊断中必须要考虑到哈夫病,避免漏诊误诊甚至延误病情。

表 2 治疗前、后实验室指标比较(n=66)

Table 2 Comparison of laboratory tests before and after treatment(n=66)

	Before	After	P values
Direct bilirubin(umol/L)	4.2± 1.6	3.6± 1.5	0.005
Indirect bilirubin(umol/L)	6.8± 3.9	4.9± 3.0	0.000
Alb(g/L)	44.5± 3.8	44.6± 2.9	0.983
ALT(IU/L)	47(13-316)	43.5(14-194)	0.018
AST(IU/L)	88.5(22-1554)	27.5(12-216)	0.000
CK(IU/L)	3271(223-163200)	226(46-5859)	0.000
LDH(IU/L)	303(150-2342)	324(169-1464)	0.201
Myoglobin(ng/mL)	1121.5(29.9-35974)	28.2(21-245.9)	0.000
CK-MB(ng/mL)	78.1(3.7-1676)	4.6(0.7-78.5)	0.000
Troponin T(ng/mL)	0.004(0.001-0.07)	0.005(0.001-0.042)	1.0
Bun(mmol/L)	4.6± 1.4	4.3± 1.2	0.184
Creatinne(umol/l)	63.5± 16.1	62.2± 14.5	0.988

ALT: Glutamic pyruvic transaminase, AST: Glutamic oxaloacetic transaminase, CK: Creatine phosphokinase, LDH: Lactate dehydrogenase, CK-MB: Creatine phosphokinase-MB, Bun: Usea nitrogen.

本研究发现,哈夫病潜伏期一般为 1-24 小时,主要临床表现为肌肉酸痛,症状轻重不等,可累及颈部、躯干以及四肢肌肉,伴有血清磷酸肌酸激酶、肌红蛋白、肌酸激酶同工酶明显升高,大量肌红蛋白入血经肝脏及肾脏代谢,可引起血胆红素和转氨酶升高以及肌红蛋白尿,但无明显肾功能损害,治疗 2~15 天后肌肉酸痛症状完全缓解, 复查血清肌酶较前明显下降,血胆红素及转氨酶等指标降至正常,尿检转阴,与既往文献报道一致,大多数患者症状较轻,经过支持治疗后几乎均能治愈,不留后遗症,急性肾功能损伤不常见,病情较重,继发多脏器功能衰竭,甚至死亡病例更为罕见[28,29]。

哈夫病引起横纹肌溶解的机制尚不明确。2009 年广东省爆发哈夫病后,有学者曾进行动物实验,发现 20 只老鼠在进食哈夫病患者残留的鲳鱼样本 2 h 后出现精神颓废,其中一只在进食后 22 h 死亡[18]。1997 年美国研究表明,老鼠在进食煮熟的水牛鱼汤后出现行为异常(符合肌肉损伤),同时发现老鼠膀胱内酱油色尿液[8]。因此哈夫病被认为与一种耐热性较高但尚不明确的毒素有关。有学者进一步研究认为,烹饪过程中产生毒素的可能性较小,小龙虾本身含有某种毒素能够破坏肌细胞膜[24]。该毒素的性质有待进一步研究。

哈夫病的发病率常与易感因素及个体差异有关。男性发病率是否高于女性尚有争议[24]。既往有文献指出,一次性食用水产品越多,患病风险越高,血清肌酸激酶水平越高,症状越重[18-24]。但另有一项研究表明, 有超过 500 人一次性食用龙虾 >400kg,其中仅 2 个成年人患病(发病率 <0.4%)[25],且在南京,每年接近 100 万人食用小龙虾, 小龙虾的年消费量几百万吨[27-30],但是没有大规模爆发流行的数据报道,因此食用小龙虾患哈夫病的发病率极低。

哈夫病本身相对少见,且症状较轻,预后较好,因此,在日常生活中不必引起恐慌。但随着经济条件发展,旅游事业日益旺盛, 再加上全球海鲜产品贸易交流以及消费需求的增大,哈夫病的流行地区以及发病率可能会增加。任何不明原因的横纹肌溶解病例,尤其是近期有水产品食用史,在诊断与鉴别诊断过程中必须考虑到哈夫病。疑似病例,包括症状比较轻的,均应向公共卫生行政机构报备并进一步随访调查。

参 考 文 献(References)

[1] Lentz O. Über die Haffkrankheit (About Haff disease)[J]. Med. Klin (German), 1925, 1(1): 4-8

[2] Centers for Disease Control and Prevention. Haff disease associated with eating buffalo fish-United States, 1997[D]. MMWR Morb. Mortal. Wkly. Rep, 1998, 47(50): 1091-1093

[3] Diaz J.H. Global incidence of rhabdomyolysis after cooked seafood consumption (Haff disease)[J]. Clin Toxicol, 2015, 53(5): 421-426

[4] Krishna N,Wood J. It looked like a myocardial infarction after eating crawfish.Ever heard of Haff disease [R]. La Morb Rep, 2001, 12(6): 1-2

[5] Louis JV, Sein S, Lyon C, et al. Two cases of rhabdomyolysis (Haff disease) after eating carp fish[J]. Investig Med High Impact Case Rep, 2016, 4(3): 2324709616663230

[6] Herman, Linda L, Bies, et al. Haff Disease: Rhabdomyolysis After Eating Buffalo Fish [J]. Western Journal of Emergency Medicine: Integrating Emergency Care with Population Health, 2014, 15(6): 664-666

[7] Langley RL, Bobbitt WH. Haff Disease After Eating Salmon[J]. Southern Medical Journal, 2007, 100(11): 1147-1150

[8] Buchholz U, Mouzin E, Dickey R, et al. Haff disease: From the Baltic Sea to the U.S. shore [J]. Emerging Infectious Diseases, 2000, 6(2): 192-195

[9] Dos Santos MC, De Albuquerque BC, Pinto RC, et al. Outbreak of Haff disease in the Brazilian Amazon [J]. Pan American Journal of

Public Health, 2009, 26(5): 469-470

[10] Junior OT, Roderjan CN, Neto EDC, et al. Haff disease associated with the ingestion of the freshwater fish Mylossoma duriventre (pacu-mantiega) [J]. Revista Brasileira de Terapia Intensiva, 2013, 25 (4): 348-351

[11] Yuen Y, Chen QT. Clinical analysis of 6 cases of Haff disease caused by crayfish[J]. Natl Med J China, 2001, 81(2): 1530-1531

[12] Xie P, Hu J, Huang JM, et al. Crayfish-related Haff disease rhabdomyolysis; diagnosis supported by bone scintigraphy[J]. Hell J Nucl Med, 2013, 16(1): 60-61

[13] Yi F, Yuan X G, Wang Y, et al. Clinical treatment of Food-borne rhabdomyolysis diagnosis [J]. Intern Intensive Med, 2012, 18 (6): 301-302

[14] Feng G, Luo Q, Zhuang P, et al. Haff disease complicated by multiple organ failure after crayfish consumption: A case study [J]. Rev Bras Ter Intensiva, 2014, 26(4): 407-409

[15] Gan L, Li Q, Gong NK, et al. Two cases of rhabdomyolysis diagnosis caused by eating crayfish [J]. Liaoning Med Univ, 2015, 36 (10): 111-112

[16] Shenzhen Daily. Four Hospitalized after Eating Too Much Crawfish [R]. Available online: http://www.szdaily.com/content/2016-08/09/content_13700987.htm (accessed on 30 September 2016)

[17] Zhang Bo, Yang Guang, Yu Xiang-bao, et al. Haff Disease after Eating Crayfish in East China[J]. Intern Med, 2012, 51(5): 487-489

[18] Huang X, Li Y, Huang Q, et al. A past Haff disease outbreak associated with eating freshwater pomfret in South China [J]. BMC Public Health, 2013, 13(1): 447-454

[19] Chen X.F, Huang P.P, Kang J, et al. Unexplained rhabdomyolysis: Clinical analysis of twenty three cases[J]. Chin Emerg Med, 2010, 19 (4): 1062-1065

[20] Wu J.Z. A report on the diagnosis of rhabdomyolysis caused by crayfish in China [C]. In Proceedings of the Second National Symposium on Acute and Severe Poisoning and Taishan Poisoning and Occupational Disease Summit Forum, Jinan, China, 2011, 5(1): 25-30

[21] Han L, Zhang J. Analysis of 11 cases of rhabdomyolysis syndrome caused by crayfish[J]. Intern. Intensive Med, 2011, 17(4): 314-316

[22] Tong W, Yin GL. Treatment of two cases of rhabdomyolysis caused by eating crayfish[J]. Nurs Pract Res, 2011, 8(12): 157-158

[23] Zhu L. Investigation of two crayfish cases related to rhabdomyolysis syndromes[J]. Prev Med Trib, 2015, 21: 700-703

[24] Chen Y, Yuan B, Xie G, et al. Outbreak of Haff disease caused by consumption of crayfish (Procambarus clarkii), Nanjing, Jiangsu Province[J]. Food Control, 2016, 59(1): 690-694

[25] Han LL, Xu RJ. Investigation and analysis of "crayfish incident" in Nanjing[J]. Chin Health Insp, 2012, 19(1): 75-78

[26] Yuan BJ, Wu CL, Guo BF. Analysis of 2 cases of new rhabdomyolysis syndrome in Nanjing[J]. Jiangsu Prev Med, 2013, 24(1): 43-44

[27] Zong WQ, Zhen SQ, Yuan BJ, et al. Epidemiological analysis of rhabdomyolysis syndrome caused by crayfish in Jiangsu Province during 2012 to 2014[J]. Ood Saf Qual, 2015, 6(2): 4258-4261

[28] Chan TY. The Emergence and Epidemiology of Haff Disease in China [J]. Toxins(Basel), 2016, 8(12): 351-359

[29] Zong WQ, Zheng SQ, Liu JF. One severe case report of crayfish induced rhabdomyolysis diagnosis[J]. Jiangsu J Prev Med, 2016, 27(2): 227-228

[30] Hou PS, Liu DS. We don't need to be worried about crawfish [R]. Health Manag, 2011, 2(1): 54

（上接第 5241 页）

[14] Marhold M, Tomasich E, El-Gazzar A, et al. HIF-1alpha Regulates mTOR Signaling and Viability of Prostate Cancer Stem Cells[J]. Mol Cancer Res, 2015, 13: 556-564

[15] Lee SH, Jee JG, Bae JS, et al. A Group of Novel HIF-1alpha Inhibitors, Glyceollins, Blocks HIF-1alpha Synthesis and Decreases Its Stability via Inhibition of the PI3K/AKT/mTOR Pathway and Hsp90 Binding[J]. J Cell Physiol, 2015, 230: 853-862

[16] Luo H, Guo P, Zhou Q. Role of TLR4/NF-κB in damage to intestinal mucosa barrier function and bacterial translocation in rats exposed to hypoxia[J]. PloS One, 2012, 7(10): e46291

[17] Zhou QQ, Yang DZ, LuoYJ, et al. Over-starvation aggravates intestinal injury and promotes bacterial and endotoxin translocation under high-altitude hypoxic environment [J]. World J Gastroenterol, 2011, 17(12): 1584-1593

[18] Adak A, Ghosh, Mondal KC. Modulation of small intestinal homeostasis along with its microflora during acclimatization at simulated hypobaric hypoxia[J]. Indian J Exp Biol, 2014, 52(11): 1098-1105

[19] Zhang F, Deng Z, Li W, et al. Activation of autophagy in rats with plateau stress-induced intestinal failure [J]. Int J Exp Pathol, 2015, 8 (2): 1816-1821

[20] Adak A, Maity C, Ghosh K，et al. Alteration of predominant gastrointestinal flora and oxidative damage of large intestine under simulated hypobaric hypoxia[J]. Z Gastroenterol, 2014, 52(2): 180-186