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Serum hepcidin: indication of its role as an "acute phase" marker in febrile children

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Abstract

Background: Hepcidin is classified as a type II acute phase protein; its production is a component of the innate immune response to infections.

Objective: To evaluate the alterations of serum hepcidin in children during and following an acute febrile infection.

Materials and methods: 22 children with fever of acute onset (< 6 hours) admitted to the 2nd Department of Pediatrics-University of Athens. Based on clinical and laboratory findings our sample formed two groups: the viral infection group (13 children) and the bacterial infection group (9 children). Hepcidin, ferritin and serum iron measurements were performed in all subjects.

Results: Serum hepcidin values did not differ notably between children with viral and bacterial infection, but a significant reduction of hepcidin was noted in both groups post-infection.

Conclusion: Our study provides clinical pediatric data on the role of hepcidin in the face of an acute infection. In our sample of children, hepcidin was found to rise during the acute infection and fall post-infection.

Keywords: Hepcidin, Acute infection, Children, Marker

Introduction

Hepcidin is a cytokine-induced antimicrobial peptide produced in the liver that principally regulates the homeostasis of iron concentration. Although its production can be induced by multiple stimuli, IL-6 is considered its dominant upregulator [1]. Thus hepcidin could be classified as a type II acute phase protein. The induction of hepcidin is a component of the innate immune response to infections; it decreases extracellular iron levels reducing iron availability to invading microorganisms [2].

Most studies investigate the regulation and potential roles of hepcidin in animal models [3,4]. Although hepcidin plays a key role in the development of anaemia associated with inflammation and chronic disease, there are only a few clinical studies that examine hepcidin alterations in acute or chronic infections. However, there are not sufficient data in children to validate the use of hepcidin levels in clinical algorithms for the diagnosis of acute infection.

The evaluation and treatment of children with fever without a source is a challenging and controversial clinical problem [5]. Although most well appearing children with fever have benign viral illnesses, fever might represent the first sign of occult bacteremia and subsequent serious bacterial infection [6,7]. Discrimination based on clinical criteria has not been sufficient to determine management [8].

A number of large prospective studies have established criteria to accurately identify children warranting presumptive antibiotic therapy [9,10]. Traditional laboratory screening tests include total white blood cell count, absolute neutrophil count, band to neutrophil ratio and C-reactive protein [11-13]. The use of other acute phase reactants, such as procalcitonin and IL-6, to ameliorate the sensitivity of the screen resulted in increased use of antibiotics [14-17].

During an acute-phase reaction there are dramatic changes in iron metabolism. Previous studies have demonstrated differences in serum iron parameters in children with acute bacterial versus viral infections [18]. We hypothesized that the comparison of hepcidin levels

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of children convalescing from bacterial and viral infections would not yield significant differences enhancing the role of hepcidin as an acute reactant protein. Thus the aim of the present study was to evaluate the alterations of serum hepcidin not only during the acute febrile phase but also post-infection.

Materials and methods

This longitudinal study was conducted during a three-year period between 2008 and 2011. Children of Greek origin and nationality participated voluntarily in the study. Informed consent from parents was obtained in advance. The Ethics Committee of our Hospital and the University of Athens Medical School approved the research protocol.

Among 45 patients admitted to the 2nd Department of Pediatrics-University of Athens, 22 children were enrolled in the study. The subjects' parents filled in a detailed questionnaire, with specific attention any history of anemia, chronic illness and folic acid or iron dietary supplementation. Children receiving antibiotic treatment or dietary iron supplementation as well as children with history of chronic disease or other co-morbidities were excluded from the study (18 patients). The remaining 5 febrile patients were also excluded since their infection could not be classified as viral or bacterial. All participating children underwent thorough physical examination.

The study population consisted of 22 infants and children (13 boys, mean age 28.06 ± 37.64 months, range 1 to 144 months) presenting with fever of acute onset (< 6 hours). Full blood count with differential, routine biochemical studies, C-reactive protein, hepcidin, ferritin and serum iron measurements were performed in all subjects at the time of presentation and 4 weeks later, using standard methods by the same laboratory. The hepcidin concentration samples were stored at -80°C for 5 to 10 months before analysis. Serum hepcidin-25 isoform measurements were performed by using a specific ELISA kit (DRG INTERNATIONAL Inc. 1167 U.S Highway 22 East, Mountainside, NJ 07092 USA) according to the manufacturer's instructions [19].

Based on clinical and laboratory findings our sample was divided into two groups: the viral infection group (13 children) and the bacterial infection group (9 children). The discrimination between bacterial and viral infection was based on the combination of positive blood or urine culture along with C-reactive protein >40 mg/dl and leukocytosis with neutrophilia (white blood cell count >15.000/mm^3, neutrophils >60%). The bacterial pathogens isolated were: *strep. pneumoniae, Esherichia Coli, Klebsiella pneumoniae, staph aureus*. The diagnosis of viral infection was based on either positive polymerase chain reaction (PCR) test or positive IgM antibodies for a specific viral agent (Epstein-Barr virus, cytomegalovirus, coxsackie virus, adenovirus). The clinical spectrum of febrile illnesses included upper or lower respiratory tract infections, urinary tract infections, occult bacteremia, gastroenteritis and cervical lymphadenitis.

Statistical analysis

All statistical analyses and data management were performed using STATA for Windows v 8.5, (StataCorp, Texas, USA, 2006). Data are expressed as Mean ± SD, median. Our study population formed two groups, as mentioned above, the viral infection and bacterial infection groups. Each study variable was measured during the infection (variable 1) and after the infection (variable 2). Data between the two groups (variable X-viral group vs. variable X-bacterial group) were compared using non-parametric Mann-Whitney U test (independent samples). Data within each group (variable X1 vs. variable X2) were compared using non-parametric Wilcoxon paired test (paired samples). We also calculated the difference between variable 1 and variable 2 as ΔvarX = varX1-varX2 within each group and we compared these differences between the two groups (ΔvarX-viral group vs ΔvarX-bacterial group) using non-parametric Mann-Whitney U test (independent samples). $P < 0.05$ was considered significant.

Results

All study variables are presented in Table 1. Significant differences are hereupon noted in detail. Serum hepcidin values were not notably different between children with viral and bacterial infection, but a significant reduction of hepcidin was noted in both groups post-infection. Serum ferritin values were similar among children belonging to the two groups; however, serum iron levels were found significantly lower only during the acute phase of bacterial infections. Within each group there were significant differences in ferritin and iron levels observed during and after infection. Significant increases in hemoglobin and hematocrit values were noted post-bacterial infection. The difference in hematocrit (Δhct) was significantly greater in the bacterial infection group as well as the difference in MCHC and reticulocyte percentages. As expected, initial ESR values were significantly higher in the bacterial infection group, resulting in a greater difference of ESR (ΔESR) than in the viral infection group. Similar changes were observed in WBC and neutrophil count, with higher initial values and greater differences (ΔWBC and ΔN) found in children with bacterial infections. Within each individual group initial lymphocyte count value was significantly lower, while the difference in monocyte count (ΔM) was significantly greater in the viral infection group. Initial CRP value was considerably higher in children with bacterial infections, leading to a greater difference (ΔCRP) in this group compared to the viral infection group. Differences in platelet counts within each group were significant.

Table 1 Characteristics of study population groups

Δvar = var1-var2	Viral infection (n = 13)	Bacterial infection (n = 9)	P*
Age (months)	22.8(±31.75), 8.5 (1 ~ 108)	35.66(±45.79), 18 (2 ~ 144)	
Male gender (%)	7(53.85%)	6(66.67%)	
Hepcidin1	90.52(±50.97), 79.44(11.42 ~ 210.18)	72.63(±39.95), 74.10(10.61 ~ 133.8)	0.48
Hepcidin2	53.18(±22.46), 46.17(27.12 ~ 100.73)	42.34(±28.83), 33.14(18.39 ~ 115.73)	0.12
Δhepcidin(1 → 2)	37.34(±59.89), 33.48(−89 ~ 178.74)	30.28(±38.25), 34.99(−39.44 ~ 87.61)	0.86
P**	***0.033***	***0.05***	
Ferritin1	135.98(±106.36), 68.12(30.1 ~ 333.3)	160.01(±117.97), 106.5(73.57 ~ 457.3)	0.24
Ferritin2	50.66(±37.55), 34.5(14 ~ 160)	67.65(±54.01), 39.3(12.4 ~ 173)	0.5
Δferritin(1 → 2)	85.31(±106.86), 35.58(−25.9 ~ 292.58)	92.36(±142.80), 51.7(−69 ~ 421.95)	0.71
P**	***0.0046***	***0.05***	
Serum iron1	29.69(±17.07), 28(9 ~ 69)	15.66(±4.58), 16(10 ~ 25)	***0.015***
Serum iron 2	47.69(±20.34), 46(21 ~ 76)	46.33(±27.83), 42(18 ~ 115)	0.61
ΔSerum iron (1 → 2)	−18(±29.76), −17(−67 ~ 48)	−30.66(±28.35), −24(−98 ~ 7)	0.24
P**	***0.039***	***0.01***	
Hb1(gr/dl)	11.74(±1.91), 11.7(8.1 ~ 15.5)	11.4(±1.24), 11(10.2 ~ 13.7)	0.59
Hb2 (gr/dl)	11.93(±0.92), 11.8(10.6 ~ 13.7)	12.66(±0.87), 12.1(11.7 ~ 13.9)	0.065
ΔHb(1 → 2)	−0.19(±1.63), −0.69(−2.5 ~ 3.7)	−1.26(±0.95), −1.1(−3.4 ~ −0.19)	0.17
P**	0.46	***0.007***	
Hct1 (%)	35.82(±5.62), 35.8(24.6 ~ 45.9)	34.5(±3.74), 32.9(30.3 ~ 41)	0.48
Hct2 (%)	35.30(±2.71), 35(32 ~ 40.5)	38.53(±2.48), 38.7(35.6 ~ 42)	***0.01***
Δhct(1 → 2)	0.51(±4.65), −0.70(−7.9 ~ 10.7)	−4.03(±3.02), −3.1(−10.4 ~ −1)	***0.01***
P**	0.86	***0.007***	
MCHC1	29.84(±1.58), 30(26 ~ 32.8)	29.36(±1.33), 29(27.5 ~ 31.3)	0.29
MCHC2	30.23(±1.20), 30(28 ~ 32)	30.36(±1.13), 30.2(28 ~ 32.1)	0.68
Δmchc(1 → 2)	−0.38(±1.41), −0.5(−3 ~ 2)	−1.0(±1.15), −1(−3 ~ 0.5)	0.34
P**	0.32	***0.028***	
reticulocytes1(%)	1.21(±0.66), 1(0.5 ~ 2.7)	1.6(±0.64), 1.5(0.6 ~ 2.4)	0.16
reticulocytes 2 (%)	0.86(±0.35), 0.8(0.3 ~ 1.4)	0.8(±0.36), 0.7(0.3 ~ 1.6)	0.66
Δreticulocytes (1 → 2)	0.35(±0.74), 0.3(−0.8 ~ 2.1)	0.8(±0.64), 0.6(0–1.7)	0.13
P**	0.10	***0.012***	
ESR1 (mm/1 h)	17.38(±8.11), 15(5 ~ 31)	37.66(±14.04), 38(19 ~ 70)	***0.0007***
ESR2 (mm/1 h)	11.38(±8.7), 9(4 ~ 35)	12.44(±8.5), 10(4 ~ 30)	0.68
ΔESR(1 → 2)	6.0(±12.32), 3(−15 ~ 26)	25.22(±12.36), 26(8 ~ 49)	***0.0033***
P**	0.1	***0.007***	
WBC1/mm^3	10205(±3806), 10100(4200 ~ 18200)	23133(±13813), 17400(9300 ~ 50100)	***0.005***
WBC2/mm^3	10100(±3003), 8900(6000 ~ 16800)	10855(±5008), 10400(4700 ~ 21100)	0.86
Δwbc(1 → 2)	115(±4306), 200(−6300 ~ 9700)	12277(±12920), 7700(−4000 ~ 34100)	***0.016***
P**	0.94	***0.02***	
N1 (%)	47.38(±24.59), 54(11 ~ 89)	69.55(±16.43), 66(40 ~ 89)	***0.02***
N2 (%)	37.07(±11.62), 35(21 ~ 63)	37.17(±15.87), 41(10 ~ 55)	0.73
ΔN(1 → 2)	10.3(±18.19), 16(−24 ~ 33)	37.37(±18.42), 37(−1 ~ 56)	***0.01***
P**	0.063	***0.0109***	
L1 (%)	37.3(±23.08), 33(5 ~ 72)	19.88(±10.44), 23(6 ~ 33)	0.08

Table 1 Characteristics of study population groups *(Continued)*

L2 (%)	49.61(±14.20), 52(27 ~ 72)	48.63(±18.18), 45(32 ~ 82.5)	0.78
ΔL(1 → 2)	−12.3(±18.71), −17(−39 ~ 24)	−28.74(±16.85), −28(−55.5 ~ −7)	0.065
P**	***0.042***	***0.007***	
M1 (%)	12.38(±5.79), 12(6 ~ 24)	8.66(±5.52), 6(3 ~ 20)	0.069
M2 (%)	8.23(±2.80), 7(4 ~ 13)	10.03(±3.45), 10(6 ~ 16)	0.19
ΔM(1 → 2)	4.15(±6.4), 2(−4 ~ 18)	−1.36(±6.39), −3(−10 ~ 10)	***0.034***
P**	0.072	0.4	
CRP1 (mg/dl)	17.07(±24.69), 12(0 ~ 93)	100.88(±59.50), 92(24 ~ 178)	***0.0006***
CRP2 (mg/dl)	4.57(±5.48), 1(0 ~ 17)	5.11(±9.51), 2(0 ~ 30)	0.91
Δcrp(1 → 2)	12.5(±23.08), 7(−9 ~ 82)	95.77(±64.87), 90.5(−6 ~ 173)	***0.0037***
P**	***0.022***	***0.0109***	
PLT1 /mm^3	382923(±162607), 335000(191000 ~ 758000)	465444(±162687), 438000(215000 ~ 709000)	0.19
PLT2 /mm^3	275538(±63602), 278000(198000 ~ 403000)	302555(±48844), 303000(230000 ~ 383000)	0.25
ΔPLT(1 → 2)	107384(±137673), 44000(−84000 ~ 355000)	162888(±132197), 120000(−41000 ~ 326000)	0.3
P**	***0.015***	***0.0109***	

P* Mann-Whitney U test.
P** Wilcoxon paired test.
Data are expressed as mean (±SD), median.

Discussion

Our study provides clinical pediatric data on the role of hepcidin in the face of an acute infection. In our sample of children with viral and bacterial infections, hepcidin was found to rise during the acute infection and fall post-infection.

Hepcidin is a 25-amino acid peptide synthesized by hepatocytes, secreted into the bloodstream and cleared from the circulation by the kidneys. It regulates the levels of circulating iron by controlling the absorption of dietary iron and the release of iron from macrophages and hepatocytes. Hepcidin synthesis is regulated by both physiologic and pathologic mechanisms. In peripheral blood leads in decrease in hepcidin concentration In hypoxia, iron deficiency, anemia or ineffective erythropoiesis, increased iron demand in the peripheral blood leads to a decrease in hepcidin concentation. The latter results in increased absorption of iron from the intestine and increased release from iron-storing cells by binding, internalization and degradation of the cellular iron efflux molecule, ferroportin [20].

On the contrary, infection, chronic inflammation and iron overload result in increases of hepcidin concentration and subsequent decreases in circulating iron; in hereditary hemochromatosis a mutated hepcidin gene results in deficient excretion of the molecule leading to iron accumulation.

Most studies examining the role of hepcidin as an acute phase protein are based on in vitro and animal models. Specifically, hepcidin has been well described as a hepatic acute phase protein in laboratory studies similarly to ferritin. Ferritin rises during acute infections resulting in unreliable measurements as an iron parameter. Murine models indicate that hepcidin is a component of the innate immune response to acute infection with anti-inflammatory properties and a potential marker of billiary stress [21,22]. Experimental deliberate exposure to bacterial agents in salmon and rats has demonstrated the up regulation of hepcidin [23,24].

Limited research data from adult populations attempt to elucidate the role of hepcidin in the common cold, iron metabolism disorders, chronic kidney disease, chronic hepatitis C and kidney transplant recipients [25-27]. In an adult patient population study group, hepcidin was demonstrated as a potentially useful marker that reflects the degree of billiary inflammation in cholecystitis and primary sclerosing cholangitis (PSC) - associated bacterial infection. To the best of our knowledge, there are only two studies examining the role of serum hepcidin during chronic infections in pediatric populations. One showed a correlation of increased hepcidin levels with asymptomatic malarial parasitemia (P. falciparum and P. vivax), despite the absence of a measurable acute phase response [28]. The second failed to demonstrate significant alterations of hepcidin levels in children with chronic gastrointestinal infections (*H. pylori* and helminthes) [29].

The main limitation of our study was the small size of sample. However, since weak statistical significance was achieved, a larger sample is needed to clarify the changes in hepcidin levels. The comparison of its levels in children convalescing from bacterial and viral infections did not yield significant differences. Interestingly, low levels of serum iron were shown in bacterial infections. These findings generate thoughts about the existence of other biological parameters involved in the regulation of iron metabolism during acute infection.

Conclusions

The present study provides preliminary data on the role of hepcidin as an acute reaction marker in febrile children. Further studies are needed to clarify our findings, ideally in a larger sample of febrile children. In addition other biological parameters involved in iron metabolism could be investigated.

Abbreviations

Hb: Hemoglobin; Ht: Hematocrit; MCHC: Mean corposcular hemoglobin concentration; ESR: Erythrocyte sedimentation rate; WBC: White blood cells; N: Neutrophils; L: Lymphocytes; M: Monocytes; CRP: C-reactive protein; PLT: Platelets.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LK: design the study and enroll the subjects. AS: participated in the selection of the subjects. DG: measured the serum hepcidin samples. LS: measured the serum hepcidin samples. CT: did the statistical analysis. All authors read and approved the final manuscript.

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