

川崎病急性期白细胞介素-6、N端脑钠肽前体和铁蛋白变化的临床意义

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摘 要 **目的** 观察川崎病患儿急性期血清白细胞介素-6(IL-6)、N端脑钠肽前体(NT-proBNP)和铁蛋白的变化,探讨其在辅助诊断川崎病中的意义,与丙种球蛋白(IVIG)无反应和冠状动脉损害(CALs)的关系。**方法** 选取2014年10月~2016年2月在笔者医院儿科住院的急性期川崎病患儿108例为研究对象(男性64例,女性44例),年龄2月龄~11岁5月龄。根据发热10天内使用IVIG的效果,分为IVIG敏感组(81例)和IVIG无反应组(27例);并根据有无冠状动脉损伤分为CALs组(31例)和非CALs组(nCALs,77例)。选取同期住院的感染发热患儿30例为对照组(男性18例,女性12例);患者年龄4月龄~10岁。应用电化学发光法检测患儿入院当天血清IL-6和NT-proBNP水平,免疫比浊法检测铁蛋白水平。比较分析川崎病急性期与对照组、IVIG敏感组和IVIG无反应组以及CALs和nCALs组各指标的变化,对两组间比较差异有统计学意义的指标进行受试者工作特征(receiver operating characteristic,ROC)曲线分析。**结果** (1)川崎病患儿急性期血清IL-6、NT-proBNP和铁蛋白水平分别为 $135 \pm 268 \text{ ng/L}$ 、 $1008 \pm 1675 \text{ ng/L}$ 和 $227 \pm 238 \mu\text{g/L}$,均高于对照组 $27 \pm 29 \text{ ng/L}$ ($t = 2.192, P = 0.03$), $109 \pm 100 \text{ ng/L}$ ($t = 5.463, P = 0.000$)和 $72 \pm 101 \mu\text{g/L}$ ($t = 3.437, P = 0.001$)。(2)IVIG敏感组和IVIG无反应组中IL-6和铁蛋白水平,差异无统计学意义。IVIG无反应组NT-proBNP水平 $1837 \pm 2666 \text{ ng/L}$ 明显高于IVIG敏感组 $721 \pm 1032 \text{ ng/L}$ ($t = 3.108, P = 0.002$)。(3)CALs组和nCALs组血清IL-6水平,差异无统计学意义。CALs组NT-proBNP $1703 \pm 2569 \text{ ng/L}$ vs $742 \pm 1080 \text{ ng/L}$,铁蛋白 $340 \pm 405 \mu\text{g/L}$ vs $183 \pm 99 \mu\text{g/L}$,水平高于nCALs组(P 均 < 0.05)。(4)IL-6、NT-proBNP和铁蛋白辅助诊断川崎病的ROC曲线下面积分别为0.773、0.835和0.793。NT-proBNP判断川崎病-IVIG无反应的ROC曲线下面积为0.623。NT-proBNP和铁蛋白判断CALs的ROC曲线下面积分别为0.612和0.671;铁蛋白判断CALs的ROC曲线下面积甚至优于NT-proBNP,临界值 $160.2 \mu\text{g/L}$ 时,判断CALs的敏感度和特异性分别为73.7%和52.1%。**结论** 川崎病患儿急性期血清IL-6、NT-proBNP和铁蛋白水平显著增加,可作为辅助川崎病早期诊断的参考指标;IVIG组和CALs组患儿高血清NT-proBNP或铁蛋白水平,为预测川崎病IVIG无反应和CALs提供依据。

关键词 黏膜皮肤淋巴结综合征 免疫球蛋白 冠状动脉疾病

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Clinical Significance of Circulation Interleukin 6, N-terminal Pro-brain Natriuretic Peptide and Ferritin in Acute Kawasaki Disease.

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Abstract Objective To detect serum interleukin 6(IL-6), N-terminal pro-brain natriuretic peptide (NT-proBNP) and serum ferritin in acute Kawasaki disease (KD), and explore their values in the diagnosis of KD, and further to explore the relationship with intravenous immunoglobulin (IVIG) unresponsiveness and coronary arterial lesions (CALs). **Methods** Totally 108 patients with KD (81 IVIG responders and 27 IVIG non-responders, 31 with CALs and 77 non-CALs) were recruited from October 2014 to February 2016 at Department of Pediatrics of Tongji Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, 64 were boys and 44 were girls. Their ages ranged from 2 months to 11 years and 5 months. A total of 30 children with respiratory tract infection were selected as the control group, 18 were boys and 12 were girls, ages ranged from 4 months to 10 years. Serum IL-6, NT-proBNP and serum ferritin were measured at the day of admission. The differences between groups were analyzed by t -test. To compare the power of serum level of interleukin 6(IL-6), N-terminal pro-brain natriuretic peptide (NT-proBNP) and serum ferritin levels in predicting KD, IVIG unresponsiveness and CALs, receiver-operating characteristic (ROC) curves were plotted and areas under the curve (AUC)

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were calculated. All data are presented as means $\pm$ standard deviation. **Results** (1) The levels of IL-6 $135 \pm 268 \text{ ng/L}$, NT-proBNP $1008 \pm 1675 \text{ ng/L}$ and ferritin $227 \pm 238 \mu\text{g/L}$ were significantly higher in the acute phase patients with KD than those of the control group $27 \pm 29 \text{ ng/L}$ for IL-6 ($t = 2.192, P = 0.03$), $109 \pm 100 \text{ ng/L}$ for NT-proBNP ($t = 5.463, P = 0.000$) and $72 \pm 101 \mu\text{g/L}$ for ferritin ($t = 3.437, P = 0.001$). (2) The levels of NT-proBNP $1837 \pm 2666 \text{ ng/L}$ in IVIG unresponsive group were significantly higher than those of the IVIG responsive group $720 \pm 1032 \text{ ng/L}$ ($t = 3.108, P = 0.002$). However, there were no significant difference of IL-6 and serum ferritin between the two groups. (3) The levels of NT-proBNP in CALs group $1703 \pm 2569 \text{ ng/L}$ vs $742 \pm 1080 \text{ ng/L}$, serum ferritin $340 \pm 405 \mu\text{g/L}$ vs $183 \pm 99 \mu\text{g/L}$ were significantly higher than those of the non-CALs group ($P < 0.05$). However, there was no significant difference of IL-6 between the two groups. (4) The area under the curve for predicting KD with various variables were as follows: serum IL-6 0.773, NT-proBNP 0.835 and serum ferritin 0.793. The area under the curve for predicting resistance to IVIG with serum NT-proBNP was 0.623. The area under the curve for predicting CALs with various variables were as follows: NT-proBNP 0.612 and ferritin 0.671. The ROC of ferritin for predicting CALs is better than NT-proBNP. A ferritin cut-off value of $160.2 \mu\text{g/L}$ yielded a sensitivity of 73.7%, specificity of 52.1%. **Conclusion** The serum IL-6, NT-proBNP and serum ferritin can be used as useful parameters in early diagnosis of KD. Elevated NT-proBNP or serum ferritin may be useful to predict IVIG resistance and CALs in KD patients.

Key words Mucocutaneous lymph node syndrome; Immunoglobulin; Coronary artery disease

川崎病(Kawasaki disease, KD)又称黏膜皮肤淋巴结综合征,是一种自限性免疫性全身血管炎,早期使用大剂量丙种球蛋白(IVIG),可以使冠状动脉损伤(coronary artery lesions, CALs)由 15%~25% 减低至 3%~5%,但仍然有 10%~15% 患儿对丙种球蛋白无反应,且这部分患儿更易合并冠状动脉病变^[1,2]。早期积极地预测丙种球蛋白无反应川崎病将有助于临床治疗,从而降低冠状动脉损害率。本研究旨在综合分析以下方面:①川崎病急性期血清白细胞介素-6(IL-6)、N 端脑钠肽前体(NT-proBNP)和血清铁蛋白的变化,探讨其在辅助川崎病早期诊断的作用;② IL-6、NT-proBNP 和血清铁蛋白与川崎病-IVIG 无反应的关系;③ IL-6、NT-proBNP 和血清铁蛋白与川崎病-CALs 的关系,结果报告如下。

对象和方法

1. 对象:选取的川崎病患儿均符合美国心脏协会推荐的川崎病诊断标准^[1],并且发病 10 天内均接受大剂量丙种球蛋白(2 g/kg)和口服阿司匹林的治疗。包括男性 64 例,女性 44 例;患儿年龄 2 月龄~11 岁 5 月龄。根据发热 10 天内使用 IVIG 的效果,分为 IVIG 敏感组(81 例)和 IVIG 无反应组(27 例);并据心脏彩超检查的结果,分为 CALs 组 31 例, nCALs 组 77 例。选取同期在笔者医院儿科住院伴有发热的呼吸道感染患儿 30 例作为对照组,通过心肌酶谱、心电图检查排除心肌受累的患儿。男性 18 例,女性 12 例;患儿年龄 4 月龄~10 岁;其中诊断上呼吸道感染 23 例,支气管炎 5 例,支气管肺炎 2 例。川崎病患儿与对照组在性别、年龄方面差异无统计学意义。本研究程序均遵循笔者医院医学伦理委员会所制定的伦

理学标准并得到该委员会的批准,均取得研究对象家长的知情同意。

2. 诊断标准与治疗:丙种球蛋白无反应性川崎病诊断标准:在发病 10 天内接受大剂量丙种球蛋白 2 g/kg 治疗后 36h 发热不退($\geq 38^\circ\text{C}$),或应用丙种球蛋白 2~7 天(甚至 2 周)后再次出现发热,符合至少 1 项川崎病诊断标准者^[1,2]。CALs:依据心脏彩超检查结果,左冠状动脉与主动脉瓣环比值 ≥ 0.21 和(或)右冠状动脉与主动脉瓣环比值 ≥ 0.17 为冠状动脉受损。

3. 方法:入院当天抽取川崎病和对照组患儿静脉血共 3ml,应用电化学发光法检测患儿入院当天血清 IL-6 和 NT-proBNP 水平,免疫比浊法检测铁蛋白水平。108 例患儿在急性期(病程 1~2 周)、病程 4 周和 8 周均进行心脏超声检查,有 CALs 者随访至病程 6 个月,主要进行心脏彩超和心电图检查。

4. 统计学方法:采用 SPSS 19.0 统计学软件进行统计分析。对计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,计数资料以例数和百分比(%)表示。两组数据率的比较采用 χ^2 检验,两组样本(川崎病急性期和对照组, IVIG 无反应和 IVIG 敏感组, CALs 和 nCALs 组)中 IL-6、NT-proBNP 和铁蛋白的比较均采用独立样本 t 检验,对组间比较差异有统计学意义的指标进行 ROC 曲线面积分析,以 $P < 0.05$ 为差异有统计学意义。

结 果

1. 急性期川崎病患儿血清 IL-6、NT-proBNP 和铁蛋白水平变化:川崎病患儿急性期血清 IL-6、NT-proBNP 和铁蛋白水平均高于对照组,差异有统

计学意义 (P 均 <0.05 , 表 1)。

组别	n	白细胞介素 -6 (ng/L)	N 端脑钠肽前体 (ng/L)	铁蛋白 ($\mu\text{g/L}$)
对照组	30	27 ± 29	109 ± 100	72 ± 101
川崎病组	108	135 ± 268	1008 ± 1675	227 ± 238
t		2.192	5.463	3.437
P		0.030	0.000	0.001

2. IVIG 无反应组和 IVIG 敏感组以及 CALs 组和 nCALs 组 IL - 6、NT - proBNP 和铁蛋白变化:川崎病患儿急性期,IVIG 敏感组和 IVIG 无反应组中 IL - 6 和铁蛋白水平,差异无统计学意义。IVIG 无反应组 NT - proBNP 水平高于 IVIG 敏感组,差异有统计学意义 ($P < 0.01$)。CALs 组和 nCALs 组血清 IL - 6 水平,差异无统计学意义。CALs 组 NT - proBNP 和铁蛋白水平高于 nCALs 组,差异有统计学意义 (P 均 < 0.05 , 表 2)。

组别	n	白细胞介素 -6 (ng/L)	N 端脑钠肽前体 (ng/L)	铁蛋白 ($\mu\text{g/L}$)
IVIG 无反应组	27	226 ± 466	1837 ± 2666	257 ± 287
IVIG 敏感组	81	103 ± 137	721 ± 1032	215 ± 216
CALs 组	31	121 ± 140	1703 ± 2569	340 ± 405
nCALs 组	77	141 ± 308	742 ± 1080	183 ± 99
t_1		1.959	3.108	0.658
P_1		0.053	0.002	0.513
t_2		0.34	2.707	2.513
P_2		0.735	0.008	0.014

t_1 值及 P_1 值:IVIG 无反应组与 IVIG 敏感组比较; t_2 值及 P_2 值: CALs 组与 nCALs 组比较

3. IL - 6、NT - proBNP 和铁蛋白辅助诊断川崎病的 ROC 曲线分析:IL - 6 辅助诊断川崎病的 ROC 曲线下面积为 0.773,渐近 95% CI 为 0.674 ~ 0.872,取临界值 27.93ng/L 时,敏感度和特异性分别为 71.4% 和 73.3%。NT - proBNP 辅助诊断川崎病的 ROC 曲线下面积为 0.835,渐近 95% CI 为 0.755 ~ 0.915,取临界值 198ng/L 时,敏感度和特异性分别为 73.3% 和 90%。铁蛋白辅助诊断川崎病的 ROC 曲线下面积为 0.793,渐近 95% 置信区间为 0.683 ~ 0.903,取临界值 133.35 $\mu\text{g/L}$ 时,敏感度和特异性分别为 70.1% 和 66.7% (图 1)。

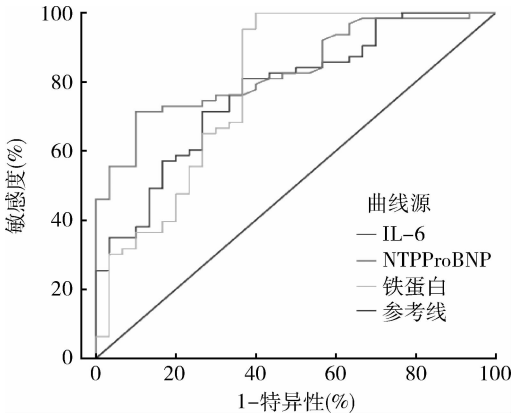


图 1 白细胞介素 -6、N 端脑钠肽前体和铁蛋白辅助诊断川崎病的 ROC 曲线

4. IL - 6, NT - proBNP 和铁蛋白判断川崎病 IVIG 无反应和 CALs 的 ROC 曲线:对两组间比较差异有统计学意义的指标进行 ROC 曲线分析发现,NT - proBNP 判断川崎病 IVIG 无反应的 ROC 曲线下面积为 0.623。NT - proBNP 和铁蛋白判断 CALs 的 ROC 曲线下面积分别为 0.612 和 0.671;由此可见,铁蛋白判断 CALs 的 ROC 曲线下面积甚至优于 NT - proBNP,取临界值 160.2 $\mu\text{g/L}$ 时,敏感度和特异性分别为 73.7% 和 52.1%。

5. 川崎病急性期 IVIG 无反应患儿 CALs 的发生率:本组患儿急性期和亚急性期(4 周内)CALs 发生率为 28.7% (31/108),IVIG 无反应组 CALs 发生率高达 40.7% (11/27);8 周后持续 CALs 的发生率降至 8.3% (9/108),IVIG 无反应组降至 22.2% (6/27);6 个月后持续 CALs 的发生率 2.8% (3/108),3 例均为 IVIG 无反应组患儿(表 3)。

表 3 川崎病急性期两种球蛋白 (IVIG) 无反应与冠状动脉损伤 (CALs) 的关系

组别	4 周内		8 周		6 个月	
	CALs	nCALs	CALs	nCALs	CALs	nALs
IVIG 无反应组	11	16	6	21	3	24
IVIG 敏感组	20	61	3	78	0	81
合计	31	77	9	99	3	105
χ^2	58.593		135.333		90.500	
P	0.000		0.000		0.000	

讨 论

目前较多研究探索川崎病早期诊断、预测 IVIG 无反应及 CALs 的指标,但尚无确切定论。研究发现炎症因子 IL - 6 与冠状动脉炎的形成有关,可能为 IVIG 无反应的预测因子^[4]。脑钠肽 (BNP) 和 NT -

proBNP 是心力衰竭的敏感指标^[5,6]。NT - proBNP 可作为川崎病早期诊断的生物学标志物,与 IVIG 无反应和 CALs 密切相关^[7-9]。而炎症状态,活化的巨噬细胞分泌大量的血清铁蛋白,川崎病并发巨噬细胞活化综合征患者血清铁蛋白显著升高,而铁蛋白在川崎病中的作用研究甚少^[10-12]。本研究结果发现,108 例急性期川崎病患儿血清 IL - 6、NT - proBNP 和铁蛋白水平与一般呼吸道感染性患儿相比显著升高,差异有统计学意义,并且具有较高的敏感度和特异性,可以与一般发热性呼吸道疾病相鉴别,尤其是 NT - proBNP 和血清铁蛋白,可作为辅助川崎病早期诊断的参考指标。

IVIG 无反应川崎病患儿发生 CALs 的危险程度更高,已经得到国际认同,但发生率国内外报道不一,可能与地域、判断标准不同有关。在本研究中,尽管于病程 10 天内进行 IVIG 治疗,本组患儿急性期和亚急性期 CALs 发生率为 28.7%,IVIG 无反应性 KD - CALs 发生率高达 40.7%;8 周后持续 CALs 的发生率降至 8.3%,IVIG 无反应组降至 22.2%;6 个月后持续 CALs 的发生率 2.8%,均为 IVIG 无反应患儿。本组病例 4 周内 CALs 发生率较高,可能与 CALs 判定标准有关。但是,尽管一过性 CALs 的发生率较高,早期 IVIG 治疗使远期 CALs 减少至 2.8%。因此,早期识别此患儿并给予积极治疗,可改善患儿的预后。国内外对 IVIG 无反应的预测指标有较多研究^[13-16]。但迄今为止,仍无发现特异性的预测指标。本研究结果显示,川崎病患儿急性期,IVIG 无反应组 NT - proBNP 水平明显高于 IVIG 敏感组,ROC 曲线下面积为 0.6 以上。提示高血清 NT - proBNP 是 IVIG 无反应的危险因素,为临床预测川崎病 - IVIG 无反应提供更多的依据,对于高血清 NT - proBNP 患儿入院后应采取更积极的治疗,缩短病程,减少住院周期,减少远期 CALs 的发生,改善预后。IL - 6 和铁蛋白均值高于 IVIG 敏感组,但差异无统计学意义,与 Sato 等^[4]和 Yamamoto 等^[11]的研究不符,可能与患儿的地域差异、遗传背景、样本的数量等有关。需进行大样本的回顾性分析。

影响川崎病远期预后的并发症主要是 CALs,尤其是冠状动脉瘤。近年来研究表明,川崎病急性期存在左心舒张功能不全,刺激心肌细胞分泌 BNP 和 NT - proBNP,川崎病急性期 NT - proBNP 显著升高,CALs 的患儿明显高于无 CALs 的患儿,与本研究结果一致。在系列高危因素中,NT - proBNP 可作为

CALs 的独立预测指标^[9,17]。值得注意的是,本研究首次发现血清铁蛋白水平在 CALs 的患儿明显高于无 CALs 的患儿,ROC 曲线下面积甚至优于 NT - proBNP。取临界值 160.2 $\mu\text{g/L}$ 时,预测 CALs 敏感度和特异性分别为 73.7% 和 52.1%。众所周知,在炎症和感染状态血清铁蛋白水平急性升高,在自身免疫性疾病如幼年特发性关节炎(全身型),肿瘤性疾病等显著升高^[18]。1 例成人川崎病和 3 例新生川崎病中血清铁蛋白升高^[12,19]。Yamamoto 等^[11]认为血清铁蛋白是川崎病 - IVIG 无反应的有效预测指标,取值 165 ng/ml,血清铁蛋白预测 IVIG 无反应的敏感度和特异性分别为 70.4% 和 63.2%,本研究中未能得出相同的结论。川崎病是一种累及中、小血管的免疫性血管炎,已知多种细胞因子参与川崎病血管炎的形成过程。单核 - 吞噬细胞异常活化,分泌大量的 TNF - α ,进一步刺激血清铁蛋白的合成和激活血管内皮细胞。而铁蛋白可以调节血管的重构和血管的生成。进而推测血清铁蛋白可能参与川崎病病理生理过程和 CALs 的形成。但需从动物实验进一步论证。本研究从临床角度发现急性期 IVIG 治疗前血清铁蛋白是 CALs 的危险因素,可作为早期预测 CALs 的参考指标之一。

综上所述,川崎病患儿急性期血清 IL - 6、NT - proBNP 和铁蛋白水平显著增加,尤其是血清铁蛋白辅助诊断川崎病的 ROC 曲线下面积为 0.793,仅次于 NT - proBNP,是继 NT - proBNP 和 IL - 6 后又一新的辅助川崎病诊断的参考指标。IVIG 组和 CALs 组患儿高血清 NT - proBNP 以及 CALs 组患儿高血清铁蛋白水平,血清铁蛋白判断川崎病 - CALs 的 ROC 曲线下面积优于 NT - proBNP,为预测川崎病 IVIG 无反应和 CALs 提供依据。对于高血清 NT - proBNP 和铁蛋白的患儿可以早期采取积极治疗措施,进一步改善远期预后。

参考文献

- 1 Newburger JW, Takahashi M, Gerber MA, *et al.* Diagnosis, treatment, and long - term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association [J]. *Pediatrics*, 2004, 114 (6): 1708 - 1733
- 2 赵晓东,杜忠东. 川崎病专题讨论会纪要[J]. *中华儿科杂志*, 2007, 45(11): 826 - 830
- 3 Tan TH, Wong KY, Cheng TK, *et al.* Coronary normograms and the coronary - aorta index: objective determinants of coronary artery dilatation [J]. *Pediatr Cardiol*, 2003, 24(4): 328 - 335 (下转第 40 页)

- cellular antioxidant properties of astaxanthin [J]. *Int J Mol Sci*, 2016, 17(1):103
- 8 Ambati RR, Phang SM, Ravi S, *et al.* Astaxanthin: sources, extraction, stability, biological activities and its commercial applications – a review[J]. *Mar Drugs*, 2014, 12(1): 128 – 152
 - 9 Li J, Wang F, Xia Y, *et al.* Astaxanthin pretreatment attenuates hepatic ischemia reperfusion – induced apoptosis and autophagy via the ROS/MAPK pathway in mice [J]. *Mar Drugs*, 2015, 13 (6): 3368 – 3387
 - 10 Qiu X, Fu K, Zhao X, *et al.* Protective effects of astaxanthin against ischemia/reperfusion induced renal injury in mice[J]. *J Transl Med*, 2015, 13(1): 28
 - 11 Fassett RG, Coombes JS. Astaxanthin in cardiovascular health and disease[J]. *Molecules*, 2012, 17(2): 2030 – 2048
 - 12 蔡辉,张蓓蓓.心脏成纤维细胞在心肌纤维化中的作用[J].微循环学杂志,2014,24(4):80 – 82
 - 13 Travers JG, Kamal FA, Robbins J, *et al.* Cardiac fibrosis: the fibroblast awakens[J]. *Circ Res*, 2016, 118(6): 1021 – 1040
 - 14 Kishimoto Y, Yoshida H, Kondo K. Potential anti – atherosclerotic properties of astaxanthin[J]. *Mar Drugs*, 2016, 14(2):35
 - 15 Zhao ZW, Cai W, Lin YL, *et al.* Ameliorative effect of astaxanthin on endothelial dysfunction in streptozotocin – induced diabetes in male rats[J]. *Arzneimittelforschung*, 2011, 61(4): 239 – 246
 - 16 Lauver DA, Lockwood SF, Lucchesi BR. Disodium disuccinate astaxanthin (Cardax) attenuates complement activation and reduces myocardial injury following ischemia/reperfusion[J]. *J Pharmacol Exp Ther*, 2005, 314(2): 686 – 692
 - 17 Kim B, Farruggia C, Ku CS, *et al.* Astaxanthin inhibits inflammation and fibrosis in the liver and adipose tissue of mouse models of diet – induced obesity and nonalcoholic steatohepatitis[J]. *J Nutr Biochem*, 2016, 43: 27 – 35
 - 18 Yang Y, Bae M, Park YK, *et al.* Histone deacetylase 9 plays a role in the antifibrogenic effect of astaxanthin in hepatic stellate cells[J]. *J Nutr Biochem*, 2017, 40: 172 – 177
 - 19 Xie C, Meng M, Yin X, *et al.* Effects of astaxanthin on renal fibrosis and cell apoptosis induced by partial unilateral ureteral obstruction in rats[J]. *Nanfang Yike Daxue Xuebao*, 2013, 33(2): 305 – 308
 - 20 Zhang J, Xu P, Wang Y, *et al.* Astaxanthin prevents pulmonary fibrosis by promoting myofibroblast apoptosis dependent on Drp1 – mediated mitochondrial fission [J]. *J Cell Mol Med*, 2015, 19 (9): 2215 – 2231 (收稿日期:2017 – 04 – 27)
(修回日期:2017 – 05 – 11)
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- (上接第 35 页)
- 4 Sato S, Kawashima H, Kashiwagi Y, *et al.* Inflammatory cytokines as predictors of resistance to intravenous immunoglobulin therapy in Kawasaki disease patients [J]. *Int J Rheum Dis*, 2013, 6(2):168 – 172
 - 5 武育蓉,陈树宝,孙隰,等.现有儿科心力衰竭诊断标准及脑利钠肽对先天性心脏病合并心力衰竭的诊断价值[J].中华儿科杂志,2006, 44 (10): 728 – 732
 - 6 Stienen S, Salah K, Eurlings LW, *et al.* Targeting N – terminal pro – brain natriuretic peptide in older versus younger acute decompensated heart failure patients[J]. *JACC Heart Fail*, 2016, 4(9):736 – 745
 - 7 Lin KH, Chang SS, Yu CW, *et al.* Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta – analysis[J]. *BMJ Open*, 2015, 5(4):e006703
 - 8 Ye Q, Shao WX, Shang SQ, *et al.* Value of the N – terminal of pro-hormone brain natriuretic peptide in diagnosis of Kawasaki disease [J]. *Int J Cardiol*, 2015,178:5 – 7
 - 9 Kimata T, Mine K, Uchiyama T, *et al.* N – terminal pro – brain natriuretic peptide and risk of coronary artery lesions and resistance to intravenous immunoglobulin in Kawasaki disease[J]. *J Pediatr*, 2013, 62(6):1205 – 1209
 - 10 Wang W, Gong F, Zhu W, *et al.* Macrophage activation syndrome in Kawasaki disease: more common than we thought? [J]. *Semin Arthritis Rheum*, 2015, 44(4): 405 – 410
 - 11 Yamamoto N, Sato K, Hoshina T, *et al.* Utility of ferritin as a predictor of the patients with Kawasaki disease refractory to intravenous immunoglobulin therapy[J]. *Mod Rheumatol*, 2015,25(6):898 – 902
 - 12 Nasir A, Al Tatari H, H amdan MA. Very high serum ferritin levels in three newborns with Kawasaki – like illness [J]. *Paediatr Child Health*, 2012, 17(4): 201 – 204
 - 13 Kobayashi T, Inoue Y, Takeuchi K, *et al.* Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease [J]. *Circulation*, 2006, 113(22):2606 – 2612
 - 14 Egami K, Muta H, Ishii M, *et al.* Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease[J]. *J Pediatr*, 2006,149(2):237 – 240
 - 15 Fu PP, Du ZD, Pan YS. Novel predictors of intravenous immunoglobulin resistance in Chinese children with Kawasaki disease[J]. *Pediatr Infect Dis J*, 2013,32(8):e319 – e323
 - 16 Rigante D, Andreozzi L, Fastigi M, *et al.* Critical overview of the risk scoring systems to predict non – responsiveness to intravenous immunoglobulin in Kawasaki syndrome [J]. *Int J Mol Sci*, 2016, 17 (3):278
 - 17 Kaneko K, Yoshimura K, Ohashi A, *et al.* Prediction of the risk of coronary arterial lesions in Kawasaki disease by brain natriuretic peptide[J]. *Pediatr Cardiol*, 2011,32(8):1106 – 1109
 - 18 Knovich MA, Storey JA, Coffman LG, *et al.* Ferritin for the clinician [J]. *Blood Rev*, 2009,23(3):95 – 104
 - 19 Cunha BA, Pherez FM, Alexiadis V, *et al.* Adult Kawasaki’s disease with myocarditis, splenomegaly, and highly elevated serum ferritin levels[J]. *Heart Lung*, 2010,39(2):164 – 172
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