International Immunopharmacology 39 (2016) 246–250

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Circulating midkine in children with Henoch-Schönlein purpura: Clinical implications

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ARTICLE INFO

Article history:
Received 25 April 2016
Received in revised form 30 June 2016
Accepted 28 July 2016
Available online 3 August 2016

Keywords:
Midkine
Henoch–Schönlein purpura
Henoch–Schönlein purpura nephritis
Biomarker

ABSTRACT

Background: Midkine (MK) is a heparin-binding growth factor, which behaves like a cytokine, involved in various cellular processes such as cellular proliferation, differentiation, survival, adhesion, and migration. Studies provided evidence for a role of MK in acute and chronic inflammatory processes. The association between midkine and Henoch-Schönlein purpura (HSP) has not yet been explored. The aim of our study was to investigate the potential role of midkine in children with HSP.

Methods: A total of 152 cases consisting of 92 children with HSP and 60 age- and sex-matched healthy control children were enrolled in this prospective study. Circulating midkine, IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, and IL-17A was measured in all of the 92 patients and 60 healthy controls. Midkine diagnostic value was evaluated by receiver operating characteristic (ROC) analysis.

Results: Renal involvement occurred in 36 of the 92 patients. Circulating midkine level was elevated in children with HSPN than those of patients without renal involvement and of the controls (326.58 (266.58–459.25) pg/ml versus 280.72 (233.67–384.36) pg/ml and 217.3 (198.98–243.65) pg/ml, respectively; $P < 0.05$). Midkine positively correlated with IL-4, IL-6, IL17A, IgA and IgE. The threshold MK concentration of HSPN was 295.58 pg/ml, with the sensitivity and specificity of 80.6% and 88.3%, respectively. The area under the receiver operating characteristic (ROC) curve (AUC_{ROC}) of MK was 0.902.

Conclusions: MK seems to be involved in the development of HSP. Measurement of serum levels of MK is helpful in confirming the diagnosis of HSP and predicting HSPN.

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1. Introduction

Henoch-Schönlein purpura (HSP) is one of the most common systemic small vessel vasculitis affecting children [1]. The incidence of HSP has increased in recent years, varies from 10 to 30 cases per 100,000 children younger than 17 years [2,3]. It is characterized clinically by palpable purpura, arthrocele or arthralgia, gastrointestinal symptoms and renal disease. Intussusception and central nervous system injury is rare [4]. HSP is considered to be self-limiting. The prognosis is related to the children's age and degree of renal involvement. The renal involvement is called Henoch–Schönlein purpura nephritis (HSPN), which develops in 30%–50% of patients with HSP within 4 to 6 weeks of the initial presentation [2,3,5]. HSPN presents with only hematuria and/or proteinuria of variable degree, and about 1%–17% children with HSPN progress to renal failure or end-stage renal disease [5–9]. However, the pathogenesis of HSP is not clear. Most HSP cases are preceded by an upper respiratory tract infection [10]. Anecdotal reports also describe HSP cases after vaccination and medications [11]. Usually, HSP is described as an immune complex-mediated systemic inflammatory disease, with immunoglobulin A (IgA)-dominant immune complexes deposit in the vessel walls of affected organs and in the kidney mesangium. The immune complexes could induce endothelial cell damage and leukocytoclastic vasculitis via the actions of inflammatory cytokines and recruitment of inflammatory cells [12–14]. HSP is diagnosed based on symptoms and signs and histopathological findings. Sometimes, patients with atypical manifestations are difficult to diagnose because there are no specific laboratory abnormalities.

Midkine (MK) is a heparin-binding growth factor belongs to midkine family which is composed of MK and pleotrophin (PTN), firstly defined in the early differentiation stage in embryonal life [15]. Studies revealed that MK is an angiogenic, pro-mitotic, and anti-apoptotic factor, plays various biological activities in development and cell survival, neural growth, inflammation [16–19], malignancy [20–22], and tissue repair [23–26]. MK plays important roles in chronic inflammatory

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http://dx.doi.org/10.1016/j.intimp.2016.07.032
1567-5769/© 2016 Published by Elsevier B.V.

disorders including rheumatoid arthritis [16], multiple sclerosis [17], inflammatory bowel disease [18], and kidney diseases [19]. It also has been suggested to be a promising prognostic/diagnostic marker and a potential target in many of diseases including inflammatory, malignancy, and toxic diseases [27,28]. But the possible connection between Henoch-Schönlein purpura, an inflammatory disease of the small blood vessels, and MK has not yet been explored. In the light of a lack of a gold standard disease marker for HSP, we designed this study to investigate circulating MK level in children with HSP. We also aimed to evaluate whether or not MK can be used as a novel biomarker for HSP and a predictor for renal involvement in children with HSP.

2. Materials and methods

2.1. Patients and controls

One hundred and fifty-two children were enrolled in this prospective study, with ninety-two HSP and sixty healthy children. All the enrolled patients were diagnosed within 7 days of onset and hospitalized in the Department of Rheumatology and Clinical Immunology of Qilu Children's Hospital of Shandong University. All the patients were followed up for 6 months.

The European League against Rheumatism and Pediatric Rheumatology European Society (EULAR/PReS) criteria was used to diagnose HSP: palpable purpura must be present (mandatory criterion) in association with at least one of the following: arthritis or arthralgia, diffuse abdominal pain, any biopsy showing a predominant IgA deposition and/or renal involvement (hematuria and/or proteinuria). The HSPN group comprised patients with HSP showing renal involvement (hematuria and/ or proteinuria) [1]. The patients who developed acute kidney injury, persistent proteinuria, nephritic syndrome and nephrotic proteinuria during follow-up underwent kidney biopsy. Patients with corticosteroids treatment in a month, as well as patients with other kidney disease at onset of HSP were excluded. After the first evaluation, urinalysis was repeated daily for the first week, and then once a week in the following month. Among the ninety-two HSP, thirty-six patients got renal involvement within 6 months.

Approval for this study was obtained from the Medical Ethics Committee of Qilu Children's Hospital of Shandong University. Informed consent was obtained from all the children's parents.

2.2. Analytical methods

Blood samples were collected from the healthy children and the patients before medical treatment in a fasting state. Serum was obtained from clotted (15 min, room temperature) and centrifuged (15 min, 700*g*) blood, then aliquoted and stored at −80 °C for further analysis. Serum MK concentration was detected by ELISA using a Human Midkine SimpleStep Kit (Abcam, ab193761) according to the manufacturer's instructions.

For the purpose of correlation analysis of other cytokine and MK, cytokine profiling was conducted using the Human Th1/Th2/Th17 Cytokine Kit (BD, 560484), which uses cytometric bead array (CBA) technology to simultaneously detect multiple cytokine proteins in serum. The following cytokine were detected: IL-2, IL-4, IL-6, IL-10, TNF, IFN-γ, and IL-17A.

Other laboratory indices were detected using automatic analyzers and retrieved from patients' medical records.

2.3. Statistical analysis

The data were analyzed using SPSS version 23.0 statistical software (IBM). Two-tailed $p < 0.05$ was considered statistically significant. According to the characteristics of the continuous variables, *t*-test, analysis of variance (ANOVA), Kruskal Wallis test and Mann Whitney *U* test were used. Categorical variables were compared using χ^2 test. Correlation analysis was conducted with Spearman's rank correlation test. A Bonferroni correction for multiple correlations was adopted with significance set for a *p*-value <0.0029 (0.05 divided by 17). The diagnostic ability of MK was evaluated by means of receiver operating characteristics (ROC) curve analysis. The area under the curve (AUC) was calculated. A perfect test was indicated by AUC of 1.0; an unvalued test was indicated by AUC of 0.5.

3. Results

Ninety-two HSP patients were included in the study, with 56(61%) boys, 36(39%) girls ranging in age from 1 to 13 (mean 6.76 ± 2.04) years. The median duration of symptoms at enrollment was 3.5 days (range 20 h to7 days). The duration of follow-up was six months. Among the ninety-two HSP patients, thirty-six patients developed renal involvement (HSPN) in six months, with 30 of these patients developing renal involvement during the first month and 6 patients developing renal involvement after a month. These children had isolated hematuria (3, 8.33%), isolated proteinuria (15, 41.67%) or combined hematuria and proteinuria (18, 50%). Kidney biopsy was performed on three patients who had nephrotic proteinuria. According to the ISKDC classification, one patient was in class I, two in class IIIa. No statistical differences in age and gender were observed among the HSP without renal involvement、HSPN and NC groups (all $p > 0.05$). Characteristics of all the children were showed in Table 1.

Median concentration of circulating MK was significantly elevated in HSP patients as compared to controls (291.74 (248.56–396.42) pg/ml versus 217.3 (198.98–243.65) pg/ml, $P < 0.05$), both in HSP without renal involvement and HSPN (Fig. 1). MK elevation in HSPN group was higher than in HSP without renal involvement group (326.58 (266.58–459.25) pg/ml versus 280.72 (233.67–384.36) pg/ml, $P < 0.05$).

As shown in Fig. 2 and Table 2, compared to the healthy control, the concentrations of serum IL-4, IL-6, IL-17A, IFN-γ and TNF were significantly increased, whereas the serum level of IL-10 decreased in HSP patients. We also found there was no obvious difference in the level of serum IL-2 between the patients with HSP and the control. But there were no significant differences in cytokine levels between HSP patients without renal involvement and HSPN patients. MK positively correlated with IL-4, IL-6, IL17A, IgA and IgE (Table 3). Nevertheless, the correlations between MK and IL-4, IgA, IgE were no longer significant after Bonferroni correction.

The areas under the ROC curve (AUC_{ROC}) of MK was 0.902, with the 95% confidence interval (CI) was 0.841–0.963 ($p < 0.001$). The cutoff

Table 1
Characteristics of the patients.

Index	HSP without renal involvement	HSPN
Only purpura, n (%)	14 (25)	16 (44.4)
Purpura and arthritis, n (%)	24 (42.9)	7 (19.4)
Purpura and abdominal pain, n (%)	15 (26.8)	4 (11.2)
Purpura, arthritis, and abdominal pain, n (%)	3 (5.3)	9 (25)

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