Serum levels of alpha-smooth muscle actin and c-Met as biomarkers of the degree of severity of Henoch–Schonlein purpura nephritis

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Approximately 40% of patients with Henoch–Schonlein purpura (HSP) develop Henoch–Schonlein purpura nephritis (HSPN) after 4 to 6 weeks of subcutaneous hemorrhaging. Immunoglobulin-A nephropathy (IgAN) and HSPN have numerous similarities, which can cause difficulty in correctly diagnosing the disorder during a differential diagnosis. The pathogenesis of the 2 diseases is not clear. We enrolled 137 patients with HSPN, 107 patients with IgAN, and 28 healthy (control) patients in our study. The levels of alpha-smooth muscle actin (α-SMA), c-Met, and Gal-deficient IgA1 (Gd-IgA1) in the 3 patient groups were determined and compared. The α-SMA, c-Met, and Gd-IgA1 levels and the clinical data from the patients with HSPN were analyzed for any correlations. The α-SMA and c-Met levels of the HSPN group were significantly higher than those of the IgAN and healthy control groups ($P < 0.01$). The Gd-IgA1 levels of the HSPN and IgAN groups were significantly different from the Gd-IgA1 level of the healthy control group ($P < 0.01$). The α-SMA levels of the HSPN group were positively correlated with blood urea nitrogen levels, serum creatinine levels, hematuria index, and proteinuria levels ($P < 0.01$). The c-Met levels of the HSPN group were positively correlated with the blood urea nitrogen and serum creatinine levels ($P < 0.01$). There were no significant differences among the α-SMA, c-Met, and Gd-IgA1 levels or the clinical data for the child and adult patients with HSPN. The serum levels of α-SMA and c-Met in patients with HSPN may be associated with the degree of disease severity. Gd-IgA1 is involved in the common immunologic pathogenesis of HSPN and IgAN. (Translational Research 2013;161:26–36)

Abbreviations: α-SMA = alpha-smooth muscle actin; BUN = blood urea nitrogen; ELISA = enzyme-linked immunosorbent assay; Gal = galactose; Gd-IgA1 = Gal-deficient IgA1; HGF = hepatocyte growth factor; HPF = high-power field; HSP = Henoch-Schonlein purpura; HSPN = Henoch–Schonlein purpura nephritis; Ig = immunoglobulin; IgAN = immunoglobulin A nephropathy; PBS-T = phosphate-buffered saline containing 0.05% Tween 20; PNA = peanut agglutinin; Scr = serum creatinine; SNA = *Sambucus nigra* agglutinin; VVL = *Vilsa villosa* lectin

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AT A GLANCE COMMENTARY

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Background

HSPN and IgAN have numerous similarities, which can cause difficulty in diagnosing the disorder correctly during a differential diagnosis. The pathogenesis of the 2 diseases is not clear now.

Translational Significance

We report the roles of α-SMA, c-Met, and Gd-IgA1 in the pathogenesis of HSPN and IgAN, which may develop a reference for disease identification, diagnosis, monitoring, and prognosis. We believe the article may be of particular interest to the readers of the *Journal.*

Henoch–Schonlein purpura (HSP) is one of the most common systemic vasculitides in children, causing serious clinical manifestations, such as nonthrombocytopenic purpura and abdominal and joint pain.[1,2] Approximately 40% of patients with HSP develop Henoch–Schonlein purpura nephritis (HSPN) after 4 to 6 weeks of subcutaneous hemorrhaging. The severity of renal involvement often directly affects the course and prognosis of the disease. Immunoglobulin-A nephropathy (IgAN) and HSPN have numerous similarities in pathogenesis and pathologic changes. The pathogenesis of the 2 diseases is not clear; however, several researchers have recently proposed that Gal-deficient IgA1 (Gd-IgA1) is involved in the pathogenesis of IgAN and HSPN.[3–6] Gd-IgA1 can be recognized by anti-glycan immunoglobulin (Ig)G or IgA1 antibodies, consequently forming immune complexes that deposit in the renal mesangium and induce glomerular injury. Alpha-smooth muscle actin (α-SMA) is the predominant actin isoform in vascular smooth muscle cells and plays an important role in fibrogenesis. Some researchers have reported that α-SMA expression can be considered a morphologic sign of the progression of chronic glomerulonephritis and an indicator of an unfavorable prognosis.[7] It also has been reported that the level of α-SMA expression in the kidney can predict the prognosis of renal dysfunction in children with membranoproliferative glomerulonephritis type I.[8] c-Met is the receptor for hepatocyte growth factor (HGF), which plays a key antifibrotic role. The antifibrotic and angiogenic properties of HGF are mediated through binding to c-Met.[9] Rampino et al[10] reported that c-Met is diffusely and strongly expressed in cellular crescents in crescentic glomerulonephritis. Kawasaki et al[11] detected both α-SMA and c-Met in HSPN-affected renal tissue, concluding that the expression of α-SMA in the kidney may be associated with the progression of renal injury in HSPN. However, no reports on the detection of α-SMA and c-Met in the serum of patients with HSPN are available. Our study sought to clarify whether the levels of circulating α-SMA and c-Met correlate with markers of severe renal disease by combining the 3 detection indices (α-SMA, c-Met, and Gd-IgA1) and clinical data in our analysis of the HSPN, IgAN, and healthy control groups and the child and adult groups. The goal of this study was to develop a reference for disease identification, diagnosis, monitoring, and prognosis.

MATERIALS AND METHODS

Patients. In total, 137 HSPN cases from the Kidney Internal Medicine of the Chinese and Mongolian Hospital were enrolled in our study. Sixty of the patients in our study were male, and 77 patients were female; the male-to-female ratio was 0.8:1. The average age of these patients was 28 ± 10.56 years (range, 7–64 years). Of these patients, 32 (18 male and 14 female) were aged less than 16 years, with an average age of 13.19 ± 8.13 years (range, 7–16 years). The male-to-female ratio in this group was 1:3.1. In addition to these patients, 107 patients with IgAN from the same hospital were enrolled in our study. Fifty of the 107 patients with IgAN were male and 57 were female. The ages of this group ranged from 7 to 66 years, with an average age of 34.11 ± 11.15 years. Twenty-eight healthy volunteers with an average age of 28.5 ± 5.62 years were recruited from the general population. The average ages of the HSPN, IgAN, and healthy control groups did not statistically differ in an analysis of variance ($P > 0.05$), excluding the possibility that the differences in the results were caused by differences in the ages of the groups. All of the subjects with other disorders, including hypertension, hypertensive disease, diabetes, and other chronic diseases, were excluded. This research followed the principles of the Declaration of Helsinki, the study protocol was approved by the ethics committee of Harbin Medical University, and written informed consent was obtained from all of the patients or their parents.

Antibodies. The fluorescently labeled goat anti-human IgA (alpha), goat anti-human IgG (H+L), and enzyme-linked immunosorbent assay (ELISA) kits and reagents were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The fluorescein isothiocyanate-labeled mouse anti-human IgM antibodies were purchased from Abcam Limited (Abcam, Cambridgeshire, UK). The fluorescein isothiocyanate-labeled rabbit anti-human C3