Nephromegaly in Children with Kawasaki Disease: New Supporting Evidence for Diagnosis and Its Possible Mechanism

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ABSTRACT: To measure the kidney size in children with Kawasaki disease (KD) and to delineate the condition of nephromegaly, 20 children with KD were enrolled in our study. Kidney sizes were measured during acute stage in these patients. Twenty healthy children and 15 febrile children served as healthy controls and fever controls, respectively. To delineate the possible mechanism, we also evaluated kidney volume (KV) in 13 other patients with KD during the acute phase and after the recovery phase as well as 26 healthy children. Plasma hepatocyte growth factor (HGF) and transforming growth factor-$\beta 1$ (TGF-$\beta 1$) levels were determined for all children. Kidney lengths and KV in patients with KD during the acute phase were significantly larger than those of healthy children. There was no kidney enlargement in healthy controls and after the recovery phase. The ratio of patient plasma HGF/TGF-$\beta 1$ during the acute phase and after the recovery phase correlated positively with the degree of nephromegaly in all patients. These results confirm the presence of large kidneys in children with KD. Our data also suggest that an elevated HGF/TGF-$\beta 1$ ratio may be responsible for the transient nephromegaly in these children. (*Pediatr Res* **63:** 207–210, 2008)

Kawasaki disease (KD) is an acute generalized vasculitis of unknown etiology occurring mostly in infants and young children. Dr. Tomisaku Kawasaki first reported this disease in 1967 (1) and published the first English report of 50 patients in 1974 (2). The diagnosis is confirmed by the presence of fever for at least 5 d and four of five classic features: conjunctivitis, lymphadenopathy, polymorphous rash, mucosa change, and extremities change (3). The most important issue in this disease is the correlation with subsequent cardiac complications in some cases. Currently, it is the leading cause of acquired heart disease in children in the developing countries and is reported as a potential risk factor for adult ischemic heart disease (4,5). However, there is no definitive diagnostic laboratory test available. If effective treatment is not given early in the course of the disease, coronary artery aneurysm develops in 20%–25% of cases (4,6).

Sterile pyuria in KD is one of a broad range of nonspecific clinical findings and the cause is unknown (7). This feature can mislead physicians to misdiagnose this disease as a urinary tract infection and lead to a series of workups, including ultrasound evaluation. The accidental detection of large kidneys during renal ultrasound examination in several patients with KD encouraged us to perform a prospective study to confirm this finding.

We previously showed a positive correlation between the nephromegaly and plasma hepatocyte growth factor (HGF)/ transforming growth factor-$\beta 1$(TGF-$\beta 1$) ratio in children with hepatobiliary diseases (8–10). The reciprocal change between HGF and TGF-$\beta 1$ may suggest a decreased antiproliferative effect of TGF-$\beta 1$ on renal growth and also potentiate the mitogenic action of HGF, leading to nephromegaly. Whether nephromegaly in KD is HGF/TGF-$\beta 1$ ratio–related is unknown. The purpose of this study was to measure renal size in children with KD and to correlate it with plasma HGF/TGF-$\beta 1$ ratios.

METHODS

Study design concerning nephromegaly in KD. A total of 20 children (13 boys and seven girls of between the ages of 3 and 78 mo) with KD at the National Taiwan University Hospital (Taipei, Taiwan) were enrolled in our study from February to June 2006. The diagnosis was established based on standard diagnostic guidelines for KD (2–4), including the absence of an alternative diagnosis. All patients had urine cultures with no growth of bacteria. All patients had normal renal function and no recent history of urinary tract infection. All received renal ultrasound examination to measure kidney sizes before i.v. human immunoglobulin (IVIG) administration. Twenty age- and sex-matched healthy children served as healthy controls. Fifteen febrile children (10 boys and five girls with ages ranging from 11 to 108 mo) with active infections (four pneumonia, three scarlet fever, three upper airway infection, two herpangina, one bacterial colitis, one roseola, and one ruptured appendix) served as disease controls. The timing of kidney size measurement in fever controls was on d 4–6 during the fever course.

Study design concerning the mechanism of nephromegaly. Thirteen children who met the diagnostic criteria for KD (2–4) were enrolled in another prospective study from March through September 2006. Twenty-six age- and sex-matched healthy children served as controls. All patients received IVIG at a dose of 1 g/kg/d for 2 d and subsequent acetylsalicylic acid treatment (80–100 mg/kg/d during the febrile phase followed by 3–5 mg/kg/d since defervescence). In children with KD, a renal sonogram and plasma were obtained on d 5.3 $\pm$ 1.6 of illness in the acute febrile phase before IVIG administration, as well as at 1 mo after defervescence (recovery phase). Absence of fever occurred on d 7.7 $\pm$ 1.1 of illness for these patients.

Renal ultrasonography was performed in all diseased and healthy children to measure renal size. Blood was drawn from each patient for plasma HGF and TGF-$\beta 1$ determination. After centrifugation at 1000 $\times$ *g*, ethylenediamine tetraacetic acid plasma samples were frozen at $-70°C$ until tested.

All studies were performed with informed written parental consent and approved by the Research Committee of National Taiwan University Hospital.

Kidney measurements. All sonograms were obtained by using a commercial unit from GE Medical Systems, model LOGIQ 400 (GE Medical Systems, Milwaukee, WI) with a 5.0-MHz probe. Bilateral longitudinal renal

Abbreviations: HGF, hepatocyte growth factor; **IVIG,** intravenous human immunoglobulin; **KD,** Kawasaki disease; **KV,** kidney volume

lengths (L) and maximal anteroposterior (AP) and transverse (W) diameters were measured. Kidney volumes (KV) were calculated according to the formula: $KV = 0.523 \times L \times W \times AP$ (11), and only the left kidney length and KV results were discussed. To avoid interobserver errors during the scanning and measurement, all scanning was performed by the same physician who did not know the diagnosis. Normal renal lengths for children in Taiwan were obtained from the Chu *et al.* report (12). Standard deviation score (SDS) for renal length was calculated according to the formula described previously (13). Absolute nephromegaly was defined as kidney length >mean + 2 SD for age. The degree of nephromegaly was evaluated by means of KVa/KVr, which indicated the ratio of patient KV during the acute phase and after the recovery stage of KD.

HGF and TGF-β1 assays. HGF concentrations were determined by using an enzyme-linked immunosorbent assay (ELISA) (human HGF kit; R&D Systems Inc, Minneapolis, MN). We used the ELISA with an monoclonal antibody to recognize both natural and recombinant human HGF. TGF-β1 concentrations were measured by using a human TGF-β1 kit from R&D Systems. The assay procedures were conducted according to the manufacturer's instructions, as described previously (8). All samples were measured in duplicate. Intra- and interassay coefficients of variation were 5.6% and 7.6%, respectively, for HGF, and 5.1% and 8.0%, respectively, for TGF-β1.

Statistical analysis. Data are reported as the mean ± SD when appropriate. The correlation between renal length and age or between KV and age or HGF/TGF-β1 ratio was examined by linear regression analysis. Analysis of covariance was used to examine the difference between the two regression lines. A *t* test was used to compare KVs. One-way analysis of variance followed by the Bonferroni *t* test was used for comparison of renal length SDS or HGF/TGF-β1 ratios among groups. Statistical significance was set at $p < 0.05$.

RESULTS

Figure 1 illustrates the correlation of left kidney length with age in children with KD ($y = 0.0376x + 6.6497$, $r = 0.864$, $p < 0.001$) and in the healthy children ($y = 0.0385x + 5.6372$, $r = 0.929$, $p < 0.001$). There was a significantly increased renal length in the children with KD ($p < 0.001$). Table 1 shows left KVs in these two groups of children. There was also a significantly increased KV in the children with KD ($p = 0.001$). Large kidneys in KD were indicated by an increase in both length and volume of the kidney, providing strong evidence of the manifes-
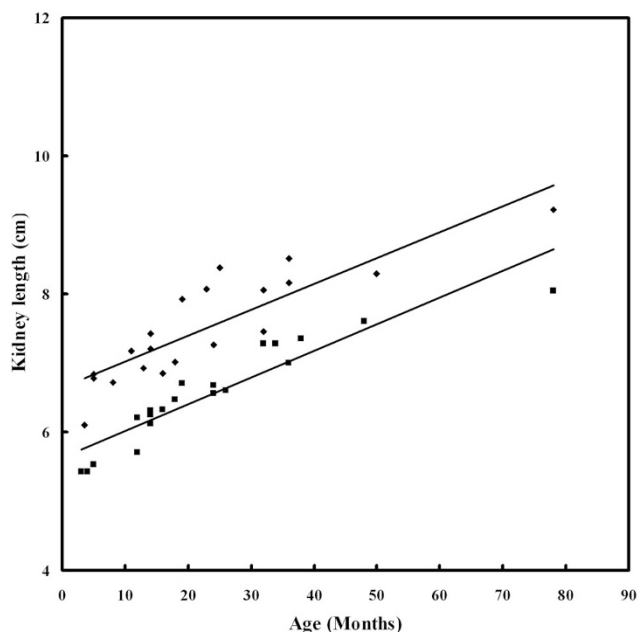
Figure 1. Regression analysis of left renal length in children with KD (♦) and in healthy children (■). Renal lengths are significantly larger in children with KD than those of healthy children. ($p < 0.001$ for the intercept and $p = 0.883$ for the slope, by analysis of covariance).

tation of nephromegaly. Analysis of right kidneys yielded similar results (data not shown).

The renal length SDS in children with KD was significantly higher than that in the fever controls or healthy children ($p < 0.001$), also indicating nephromegaly in these patients (Table 1). There was no difference between the fever controls and the healthy children. Fourteen (70%) children with KD had absolute nephromegaly. However, absolute nephromegaly was not found in either fever controls or healthy children.

Common features of KD in our children are shown in Table 2. Absolute nephromegaly is added in this table for comparison. Each feature is listed based on frequency. Polymorphous skin rash is the most common feature followed by desquamation, oral mucosa change, and conjunctivitis. Neck lymphadenopathy and nephromegaly share the same frequency thereafter.

Most children with KD were noted to have nephromegaly during the acute phase and had apparently normal-sized kidneys after the recovery phase. Figure 2 shows the comparison of KV against age in 13 children with KD during the acute phase ($y = 6.81x + 43.96$, $r = 0.630$, $p = 0.02$) and after the recovery phase ($y = 5.24x + 24.34$, $r = 0.772$, $p = 0.002$). Nephromegaly was noted significantly in children with KD during the acute phase compared with healthy children ($p < 0.001$ for the intercept and $p = 0.620$ for the slope, by analysis of covariance). Enlarged KVs returned to normal in these patients after the recovery phase ($p = 0.624$ for the intercept and $p = 0.577$ for the slope, compared with healthy children).

Plasma HGF levels were markedly elevated in children with KD during the acute phase compared with those after the recovery phase (2452 ± 2058 pg/mL *versus* 359.6 ± 53.4 pg/mL, $p = 0.003$ by paired *t* test). On the contrary, plasma TGF-β1 levels were lower during the acute phase than those after the recovery phase (25.8 ± 12.6 ng/mL *versus* 41.4 ± 18.8 ng/mL, $p = 0.017$ by paired *t* test) in these patients. Plasma HGF/TGF-β1 ratios were higher in children with KD during the acute phase than in healthy children and in patients after the recovery phase (Table 3). There also was a positive correlation between change (extent of elevation) of plasma HGF/TGF-β1 ratio and degree of nephromegaly ($y = 0.0338x + 1.354$, $r = 0.805$, $p < 0.001$; Fig. 3) for these patients.

DISCUSSION

Although KD is a multisystemic vasculitis syndrome, renal involvement is seldom mentioned and not the main characteristic of the disease. Acute renal failure has been a rare, but severe renal manifestation associated with KD (14–16). Enlarged kidneys were always reported as a finding of acute renal failure in patients with KD (14,15). In this study, most of our patients had enlarged kidneys, whereas no patients had evidence of acute renal failure (normal serum creatinine for all patients).

KD is self-limiting, but there is still a 25% risk of developing serious cardiovascular damage if proper treatment is not given early in the course of the disease (4,6). The symptoms of KD evolve over the first 10 d of illness and gradually resolve even in the absence of therapy. Because no specific or sensitive laboratory diagnostic test is available, it is a challenge for physicians to distinguish and identify this disease.

**Table 1.** *Demographic data and renal size of the study population*

	KD	Healthy children	Fever controls	*p* value
Age, mo	23.12 ± 17.78	23.55 ± 17.63	48.87 ± 35.76	
Sex, male/female	13/7	13/7	10/5	
KV, cm³	51.83 ± 17.93	35.62 ± 11.24		0.001
Renal length SDS	2.54 ± 0.97	−0.23 ± 0.82	0.15 ± 0.51	<0.001
Absolute nephromegaly,* %	70	0	0	<0.001

* Kidney length larger than mean + 2 SD for age.

Table 2. *Clinical symptoms and signs in 20 children with KD*

Symptom/sign	No. (%)
Fever ≥5 d	20 (100)
Skin rash	20 (100)
Conjunctivitis	18 (90)
Mucosal change	18 (90)
Extremities desquamation	18 (90)
Lymphadenopathy	14 (70)
Extremities induration	14 (70)
Absolute nephromegaly	14 (70)
Sterile pyuria	10 (50)
Erythema at BCG site	8 (40)
Coronary arteritis	7 (35)

BCG, bacille Calmette-Guérin.
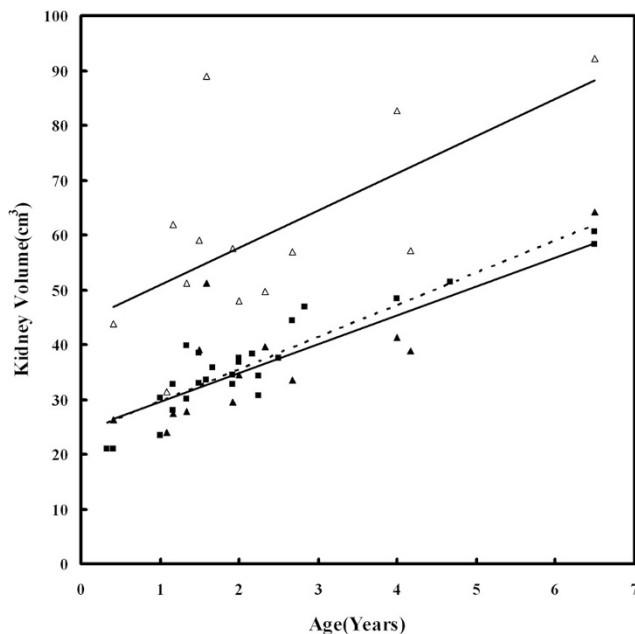
Figure 2. Regression analysis of left KV by age in children with KD during the acute phase (△) and after the recovery phase (▲, ----), and in healthy controls (■, ----). KVs in patients during the acute phase were significantly higher than those after the recovery phase ($p < 0.001$ for the intercept and $p = 0.585$ for the slope, by analysis of covariance) and those of healthy children ($p < 0.001$ for the intercept and $p = 0.620$ for the slope).

Moreover, children presenting with four manifestations of KD or presenting with coronary arterial lesions plus two to three criteria are considered as cases of atypical KD (17,18). In this situation, early identification and treatment become difficult, so awareness of other characteristics of KD for physicians may help. In addition to the diagnostic criteria of KD, other features, such as erythema at the bacille Calmette-Guérin (BCG) inoculation site, gallbladder hydrops, high white blood cell count, and platelet count, and low sodium and albumin levels are also mentioned in the literature and could help in the diagnosis of KD (18,19). In our study, up to 70% of our patients had absolute nephromegaly, occurring as frequently as neck lymphadenopathy and extremities induration, which are two of the five diagnostic criteria for KD, and the incidence of nephromegaly is significantly higher than the appearance of erythema at the BCG site. Nephromegaly in children with KD may be specific given the absence of nephromegaly in our control children with other inflammatory conditions, including three patients with scarlet fever, which is often mistaken for KD clinically.

Nardi *et al.* (14) speculated that enlarged kidneys in KD might be explained by a vasculitis involving the kidneys with resultant fibrinoid deposits and cellular infiltrations subsequently leading to ischemia followed by edema. However, this proposed mechanism seems unable to explain enlarged kidneys in our patients without renal impairment.

Increased serum HGF levels have been reported previously in children with KD (20). Elevated serum HGF concentration in these patients probably results from increased production of HGF by vascular tissue with inflammation (20). Our results confirm this finding that plasma HGF levels indeed increase in children with KD during the acute stage and return to normal after the recovery stage. These data further encourage us to continue searching for possible HGF/TGF-β1 ratio–related mechanisms for nephromegaly in KD.

We previously showed a positive correlation between nephromegaly and plasma HGF/TGF-β1 ratios in children with hepatitis or biliary atresia (8–10). This HGF/TGF-β1 ratio change has been related to nephromegaly in compensatory renal growth (9,21), and nephromegaly in acute or chronic liver diseases (8–10,21). Although the actual mechanism of HGF/TGF-β1 ratio–related nephromegaly is not yet understood, the reciprocal action of HGF and TGF-β1 with markedly increased proliferative or renotropic effect (21–24) may explain the resultant nephromegaly. In this study, we demonstrate that nephromegaly is unexpectedly common in patients with KD and it also correlates positively with patient plasma HGF/TGF-β1 ratios. This is the first report of HGF/TGF-β1 ratio–related nephromegaly in a disease other than hepatobiliary disorders. It is important to emphasize that this is currently an association in KD. It is possible that both the HGF/TGF-β1 and the nephromegaly are markers of disease severity.

Similar to children with fulminant hepatitis (8) or with biliary atresia in liver transplantation (10), nephromegaly in children with KD in the acute stage is also reversible. The change in kidney size is generally in parallel with the change in the plasma HGF/TGF-β1 ratio. Thus, our data provide a clue that, similar to children with hepatobiliary diseases, the

Table 3. *KV and laboratory data in 13 children with KD during the acute phase and after the recovery phase*

	Children with KD		Healthy children	*p* value
	Acute phase	Recovery phase		
Age, mo	28.31 ± 19.82		27.62 ± 19.07	
Sex, male/female	8/5		16/10	
KV, cm^3	60.03 ± 17.86	36.71 ± 11.22	36.9 ± 10.0	<0.001
Serum creatinine, mg/dL	0.43 ± 0.09	0.44 ± 0.09		0.368
HGF, pg/mL	2452 ± 2058	359.6 ± 53.4	506.3 ± 209.1	<0.001
TGF-β1, ng/mL	25.8 ± 12.6	41.4 ± 18.8	38.5 ± 16.7	0.053
HGF/TGF-β1, pg/ng	101.1 ± 95.4	11.6 ± 5.3	15.3 ± 6.5	<0.001
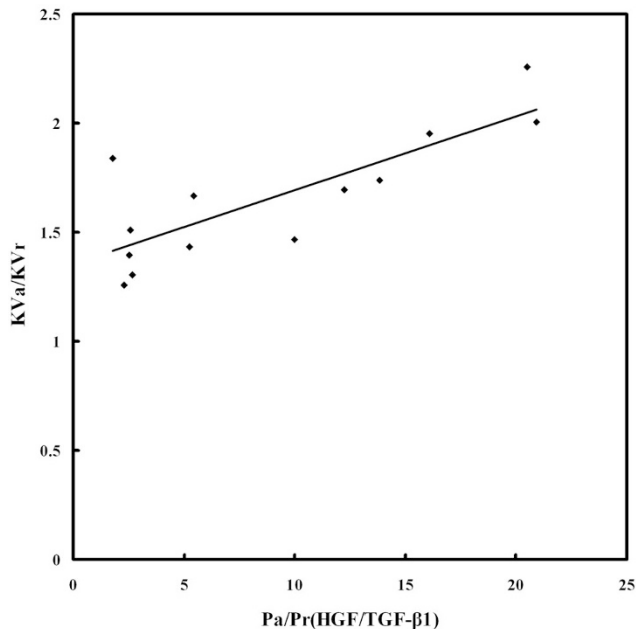
Figure 3. Regression analysis of the degree of nephromegaly on the extent of elevation of the plasma HGF/TGF-β1 ratio in children with KD (r = 0.805, $p < 0.001$). KVa/KVr indicates the ratio of the patient's KV during the acute phase and after the recovery phase. Pa/Pr (HGF/TGF-β1) indicates the ratio of the patient's plasma HGF/TGF-β1 during the acute phase and after the recovery phase.

plasma HGF/TGF-β1 ratio may also be associated with the development of nephromegaly in children with KD.

We are the first to describe nephromegaly in children with KD who do not have renal impairment. Whether our new findings can offer supporting evidence to aid in the diagnosis of KD remains to be seen. However, we suggest that all children with KD have a renal ultrasound evaluation in the acute stage, especially when the diagnostic criteria are not yet well established. From our data, we also suggest that the plasma HGF/TGF-β1 ratio may be associated with the development of nephromegaly, with the degree of resultant nephromegaly being determined by the extent of this ratio change.

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