8-2 小児 CKD へのアプローチ

- 学校検尿では蛋白尿・血尿・糖尿，および膿尿（膿尿は 2 回目以降）がチェックされる．顕微鏡的血尿は全対象の約 1%に，蛋白尿は約 0.3～0.5%に，蛋白尿血尿合併は約 0.1%に出現する．学校検尿システムはわが国の小児 CKD 対策の根幹をなすものである．
- 小児の進行した CKD の多くは先天性腎尿路疾患（congenital abnormality of kidney and urinary tract：CAKUT）であり，学校検尿では発見されにくい．
- 現在はさまざまな画像診断法がある．なかでも超音波検査は簡便・非侵襲的・安価・情報量の多さで小児では理想的である．各種画像診断法は被曝など患児側のリスク（およびコスト）ベネフィットを考えつつ計画されねばならない．

学校検尿

1．現　状

- 昭和 49 年から施行されており，小中高生までをカバーする．現在は厚生労働省管轄の 3 歳児検尿も行われている．施行後，慢性腎炎の詳細な自然歴がわかるようになり貢献度が高い．
- 学校検尿システム導入以降，糸球体腎炎を基礎疾患とするわが国の慢性腎不全患者の透析導入率が減少した．
- 顕微鏡的血尿は全対象の約 1%に，蛋白尿は約 0.3～0.5%に，蛋白尿血尿合併は約 0.1%に出現する．ただし，地域により判定のカットオフ値が異なる．
- 顕微鏡的血尿単独群から Wilms 腫瘍など緊急性のある疾患が発見される確率は非常に低い．
- 小児の CKD の疫学調査では，ステージ 3 以上の患児の 60%以上が CAKUT である．
- 学校検尿において異常が判明した患児の専門医紹介基準案をあげた（**表 15**）．日本学校保健会発行の小冊子「新・学校検尿のすべて」の改訂でより具体的になった．

表 15　専門医紹介基準

1．早朝尿蛋白および尿蛋白/クレアチニン比（g/gCr）がそれぞれ 1＋程度：0.2～0.4 g/gCr は，6～12 カ月程度で紹介． 2＋程度：0.5～0.9 g/gCr は，3～6 カ月程度で紹介． 3＋程度：1.0～1.9 g/gCr は，1～3 カ月程度で紹介． ただし，上記を満たさない場合も含めて，下記の 2～6 が出現・判明すれば，早期に専門医に相談または紹介する．
2．肉眼的血尿（遠心後肉眼的血尿を含む）
3．低蛋白血症：血清アルブミン 3.0 g/dL 未満
4．低補体血症
5．高血圧（白衣高血圧は除外する）
6．腎機能障害の存在

注）尿蛋白の検査では濃縮尿で尿蛋白/クレアチニン比が正常（<0.2g/gCr）でも陽性のことがあり，先天性腎尿路疾患などでは希釈尿で＋/－程度でも異常のことがあるため，尿蛋白/クレアチニン比の検査での上記紹介基準を推奨する．

表 16　小児でみられる腎疾患

	一次性	二次性	遺伝性・先天性
糸球体疾患	微小変化型ネフローゼ症候群 IgA 腎症 巣状分節性糸球体硬化症 急性糸球体腎炎 膜性増殖性糸球体腎炎	紫斑病性腎炎 ループス腎炎	良性家族性血尿 Alport 症候群 （そのほかの）遺伝性腎炎 先天性ネフローゼ症候群
尿細管・間質ならびに尿路系疾患		Fanconi 症候群（一次性も）	先天性水腎症 膀胱尿管逆流 低形成・異形成腎 多発性嚢胞腎 Dent 病 ネフロン癆

2. 問題点

● CAKUT は学校検尿では発見されにくい．従来から一部のモデル地区で尿中 β_2 ミクログロブリン値の測定がなされてきたが，CAKUT の発見に必ずしも良好な成績が得られていない．CAKUT を効率良く発見するには画像診断法（特に超音波検査）の導入が最も望ましい．なお，**表 16** に小児における CKD の主な原疾患をあげた．

画像診断

1. 種　類

1）単純・造影 X 線検査（排尿時膀胱尿道造影 voiding cystourethragraphy：VCUG や血管造影も含む）

単純 X 線検査で腎全体の輪郭や石灰化が評価可能である．VCUG は主として尿路感染症罹患後に行われる．現在，静脈性腎盂造影（IVP，DIP）の適応はきわめて限定される．

2）超音波検査（超音波造影剤使用も含む）

ほとんどの場合，画像診断の第一選択である．

3）CT・MRI（magnetic resonance angiography：MRA，magnetic resonance urography：MRU 磁気共鳴尿路画像も含む）

腫瘤性病変や，腸管ガスで超音波検査が困難な際にはきわめて有用である．また，急性巣状細菌性腎炎（acute focal bacterial nephritis：AFBN）の診断に造影 CT や MRI が有用である．

4）核医学（DMSA/MAG_3/DTPA シンチグラム）

DMSA（^{99}mTc-dimercaptosuccinic acid）は腎瘢痕の評価に，MAG_3（^{99}mTc-mercaptoacetyltriglycine）はレノグラムに，DTPA（^{99}mTc-diethylenetriamine pentaacetic acid）は GFR 算出やレノグラムに用いられる．

2. 判明する疾患（病態）

● 水腎症（閉塞性水腎症，膀胱尿管逆流現象（vesicoureteral reflux：VUR）を含む），水尿管，先天性巨大尿管症

● 膀胱尿管逆流現象（VCUG や超音波検査における Wax & Wane 現象や間欠的な下部尿管の描出）（**図 21**）

● 重複腎盂，重複尿管

● 嚢胞性疾患（単純性腎嚢胞，多嚢胞性異形成腎：multicystic dysplastic kidney：MCDK・多発性嚢胞腎：polycystic kidney disease：PKD

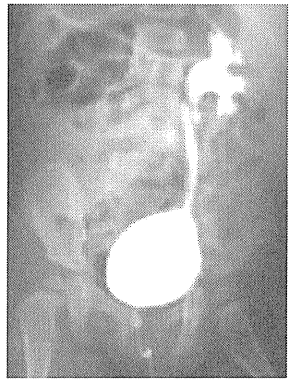

図 21　2 歳尿路感染症罹患男児の VCUG 像
左側Ⅲ度の VUR が描出されている.

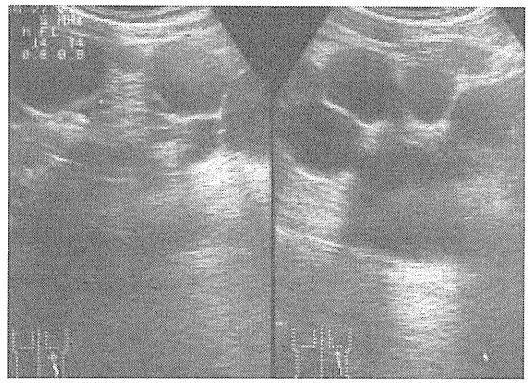

図 22　3 歳 MCDK 女児の患側腎超音波像
大小不同の嚢胞が多発している.

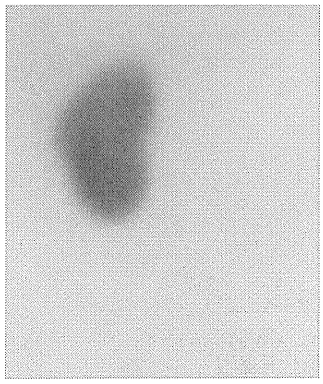

図 23　4 歳片腎男児の DMSA シンチグラム像
左腎しか描出されていない.

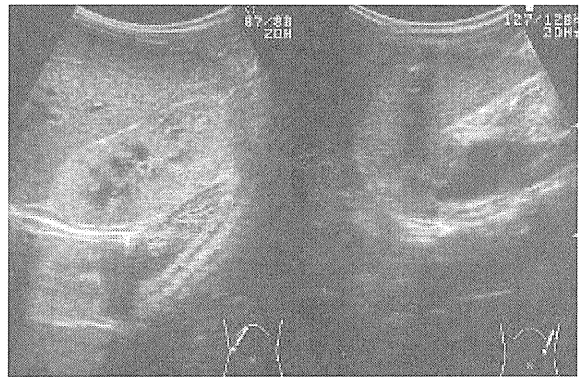

図 24　6 歳逆流性腎症男児の両腎超音波像
両腎とも小さく，輝度は上昇，右側は明らかな水腎症を呈する.

など）（図 22）

- 融合腎，異所性腎
- 矮小腎，片腎（図 23）
- 腎瘢痕
- 腎尿路結石，腎石灰化
- 腎機能障害：皮質のエコー輝度上昇（ただし乳児においては評価に注意）（図 24）
- 腎腫瘍（Wilms 腫瘍，血管筋脂肪腫など）
- デブリス：沈泥（膀胱炎，膿腎症）
- 神経因性膀胱，膀胱憩室，尿管瘤
- ナットクラッカー現象：左腎静脈が腹部大動脈と上腸間膜動脈の間で圧迫され左腎が鬱血を来たし腎杯または尿管に周囲の血管から穿破出血がおこり血尿を呈する現象
- そのほか：副腎出血，神経芽細胞腫などが偶然発見されることもある.

3. 原　則

- 小児では，成人と有病率の違いを考慮した検査プランで行う.
- 放射線被曝や肉体的・心理的負担をより考慮した検査プランで行う.
- 方法によっては超音波検査であっても患児に侵襲的でありうるという認識で行う.

4. 注意点

- 超音波検査機器により描出のされ方が微妙に異なることに注意する.
- 月齢年齢により腎の形態が異なることを認識する必要がある．例えば，乳児の腎の輪郭はやや

不整で松笠様であったり，髄質のエコー輝度が低く嚢胞様に描出されるなど．

- 核医学検査において，キットでなく自施設調整の核種を用いる際には，特に使用量過多に注意が必要である．
- 不用意な鎮静（特に長めで深い鎮静が必要な MRI 時）で事故を惹起せぬよう注意する．
- 造影剤（MRI 時も含む）使用は eGFR を十分評価して決定する．検査後の更なる腎機能障害や腎性全身性線維症（nephrogenic systemic tibrosis：NSF）を決して惹起してはならない．
- 特に VCUG はテクニックの差により被曝量が相当異なる．少しでも被曝量を減らすよう担当者は心がけねばならない．

64. 3歳児検尿を契機に診断された慢性腎不全の1男児例

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上原朋子*1*2，松山　健*2，幡谷浩史*3，本田雅敬*3

症　例

症例：初診時年齢3歳7か月，男子。
主訴：尿の泡立ち。
周産期情報：正期産児，特記事項なし。
既往歴：特記事項なし，明らかな尿路感染症の既往なし。
家族歴：特記事項なし，腎疾患の家族歴なし。
現病歴：3歳5か月の頃に，母が児の尿の泡立ちに気づいた。自宅で様子を見ていたが，持続するため精査を希望し，外来を受診した。
初診時検査結果（表1）：一般血液検査では軽度の腎機能低下を認めた。血清補体価は正常で各種自己抗体も陰性であった。尿検査では軽度の血尿と高度の蛋白尿を認めた。
初診後経過：腎機能障害の原因を調べるために画像検査を行った。腹部エコーで右腎長径4 cm，左腎長径7 cmと左右差を認めた。次いで腹部単純CTを行った（図1）ところ，同様に右腎の萎縮を認めた。水腎症や嚢胞は見られなかった。DMSAシンチグラフィーを行い（図2），%uptakeは左19.1%，右5.7%であった。両側腎下極にわずかな集積低下領域（cold region）を認めた。排泄性尿道膀胱造影（Voiding Cysto-urethrography; VCUG）を行い（図3），左Ⅲ度，右Ⅳ度の膀胱尿管逆流（vesicoureteral reflux; VUR）を認めた。蛋白/クレアチニン比で1.0前後の蛋白尿が持続したため初診から約半年後に左腎の開放腎生検を行った。光顕でび漫性メサンギウム増殖を，電顕では内皮下・上皮下・基底膜内に沈着物を認め，免疫染色でもIgG・C3の係蹄壁に沿った沈着を認めた。膜性増殖性糸球体腎炎Ⅲ型（menbranoproliferative glomerulonephritis type 3; MPGN type 3）に矛盾しない結果であった。初診時以降は尿路感染予防のための抗菌薬少量長期投与および腎機能保護のためのアンジオテンシン変換酵素阻害薬（Angiotensin-converting enzyme inhibitor; ACEI）投与を開始した。初診から3年後（6歳）にMAG3を用いた間接的VCGを行い（図4），初診時と同様に両側のVURを認めた。逆流防止術を行い，現在経過観察中である（図5）。

表1　初診時検査結果

WBC	9400/μl	Na	139mEq/l	PR3-ANCA	3.5
Hb	13.8mg/dl	K	4.5mEq/l	MPO-ANCA	1.3
Plt	33.4万/μl	Cl	110mEq/l	抗GBM抗体	＜10
		Ca	9.2mg/dl		
TP	6.2g/dl	IP	4.9mg/dl	尿所見：	
Alb	3.0g/dl			O.B.	2＋
BUN	23.5mg/dl	IgG	779mg/dl	UP	4＋
Cr	0.48mg/dl	IgA	158mg/dl	RBC	10～19/HPF
UA	5.0mg/dl	C_3	145.8mg/dl	P/Cr	4.88
		C_1	42.4mg/dl	B_2MG	1489

考　察

1）幼児の腎機能障害の原因精査に各種画像診断は有用である。

我々は，尿の泡立ちを契機に蛋白尿および腎機能障害の診断に至った症例を経験した。小児の腎機能障害の原因としては，糸球体腎炎や遺伝性腎疾患，腎尿路形成不全などが挙げられる。本症例の場合，初診時以降は有意な血尿を認めず，各種糸球体腎炎は否定的であった。腎エコーの結果，少なくとも右腎の低形成があることが示唆された。DMSAシンチグラフィーでは，右腎の%uptake低下に加えて左腎の代償性肥大を認めず，左腎にも機能障害があることが示唆された。低形成腎にはVURの合併を見ることも多いため，続いてVCUGを行ったところ，両側gradeⅢ以上の高度VURを認めた。以上の結果から，患児における腎機能障害は，胎児期からの高度VURに伴う両腎形成不全が原因と診断した。乳幼児における慢性腎不全の原因疾患のうち，第1位を占めるものは低形成／異形成腎を始めとする腎尿路発生異常である。本症例のように糸球体腎炎以外によると考えられる腎機能障害を認めた場合には，画像検査を組み合わせて形態学的異常について精査していくことが極めて有用となる場合がある。

2）両側高度VURを有する患児で適切なタイミングでの外科的治療が予後を改善する場合がある。

本症例では，両側VURとこれに伴う逆流性腎症による腎機能障害を認めた。一般的に逆流性腎症における腎機能障害は，逆行性の上部尿路感染症（upper tract infection; UTI）を反復することにより腎瘢痕化を来す，後天性の要因が主な原因とされる。本症例では，家族からの問診によれば初診時以前に明らかなUTIの既往はないということであった。しかし，通常，感冒として治療されたような，未診断UTIに繰り返し罹患していた可能性は否定できない。実際に，我々が患児に対して行ったDMSAシンチグラフィーでは，両側腎下極にわずかではあるがcold regionを認めた。これは逆行性のUTI後あるいはその反復による腎瘢痕に伴って得られる所見の一つでもある。従って，乳児期などに少なくとも1回以上のUTIの罹患があった可能性はある。

逆流性腎症に伴う腎機能低下については，上述の後天性の原因以外にも，出生前の腎発生に起因するとした報告もある。すなわちVURの存在により，胎児期の膀胱尿流動態（bladder dynamics）に異常が生じ，これが腎発生に影響するというものである。この結果，低形成腎や先天性腎瘢痕形成，二次性の組織学的変化を来したりすると報告されてい

る。

患児で見られた低形成腎や両側腎瘢痕については，胎児期の異常に基づくものである可能性も考えられる。組織所見については，過去の報告で最も高頻度に見られる病理所見は巣状の糸球体硬化症であるとされている。本症例ではMPGN typeⅢ様の組織所見であり，典型的な組織とは異なっていた。逆流性腎症において同様の所見が得られるという報告は検索し得た範囲では見られなかった。しかし，逆流性腎症の診断にはもともと腎生検を必須でないため，検索し得た文献では，必ずしも全ての症例で病理所見が得られていなかったり，比較的過去の報告が含まれたりしているといった特徴がある。従って，糸球体硬化所見以外にも，逆流性腎症における組織変化が存在している可能性は考えられる。今回得られた糸球体所見と逆流性腎症の病態との間に何らかの関連が存在する可能性も否定はできない。

患児で見られた腎機能障害は，胎児期の腎発生異常が大きく関与していた可能性が高い。2歳頃までは腎の発達成熟が続くことから，高度のVURを認めた場合には，適切な時期に外科的治療に踏み切ることで，将来の腎機能保護につながる可能性もあるものと考えられる。本症例では，診断がついてからは尿路感染予防が成功していたために，逆流防止術を行ったのは6歳時であった。その間，UTIによる腎瘢痕化は予防できていたものの，持続する圧負荷などにより，出生後の腎発生およびその後の腎機能獲得に影響していた可能性は否定できない。外科的治療のタイミングについてもう一度見直す必要があると考えた。

現時点で，逆流性腎症の患児に対する内科的治療のガイドラインは存在しないが，一般には腎保護作用を目的に，レニンアンジオテンシン経路阻害薬（rennin-angiotensin system blocker; RASB）を用いることが多いとされる。我々も初診時からACEIを併用した。今後も患児の腎機能には十分に留意する必要があるものと考える。

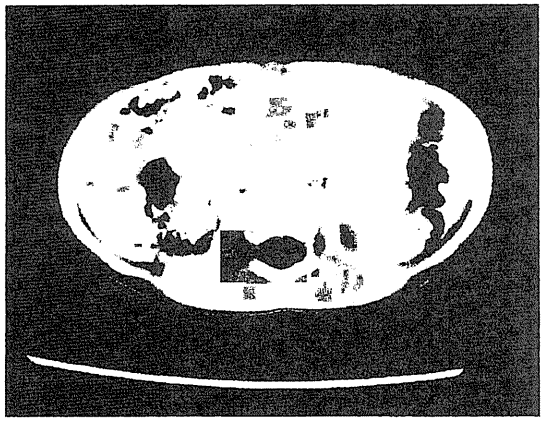


図1　腹部単純CT
右腎の萎縮を認める。嚢胞や水腎症を認めない。

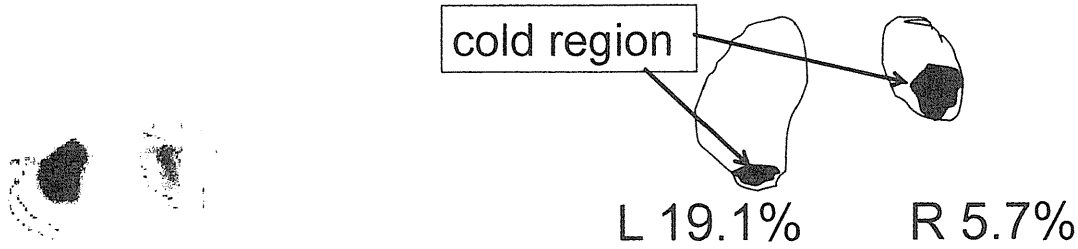


図2　DMSAシンチグラフィー
%uptake（左：右）＝19.1%：5.7%

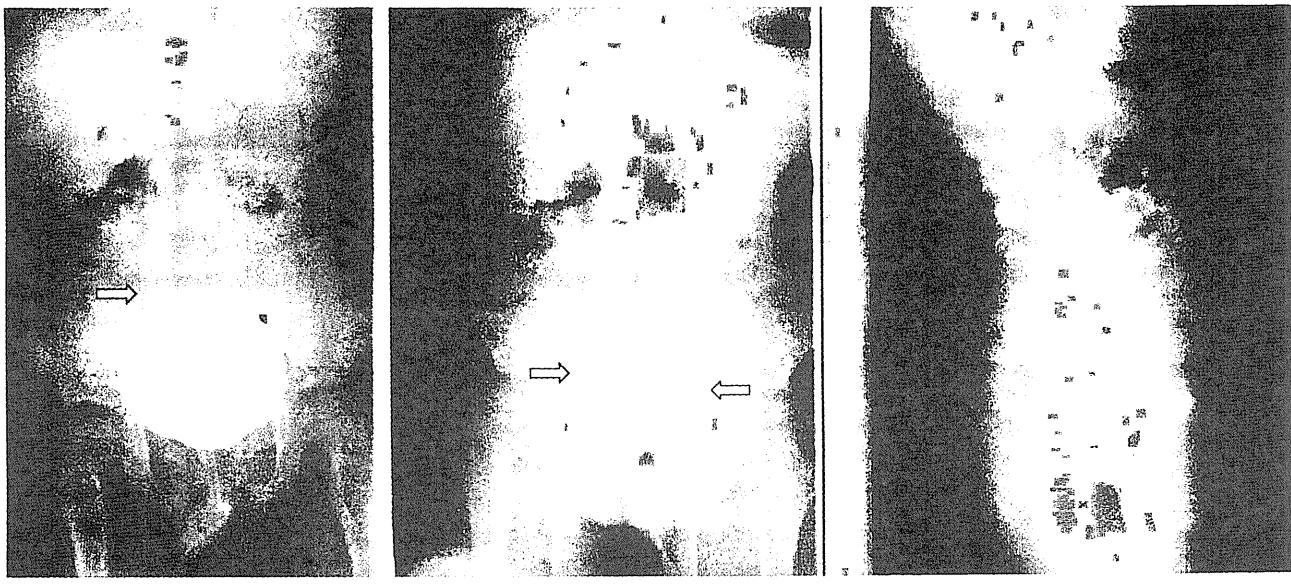
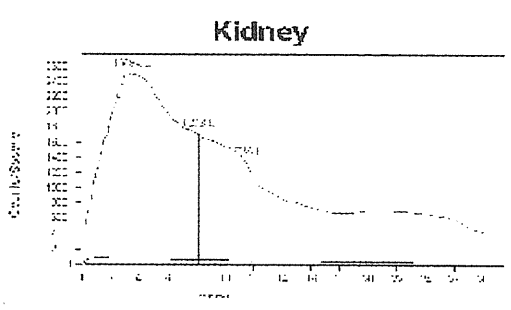
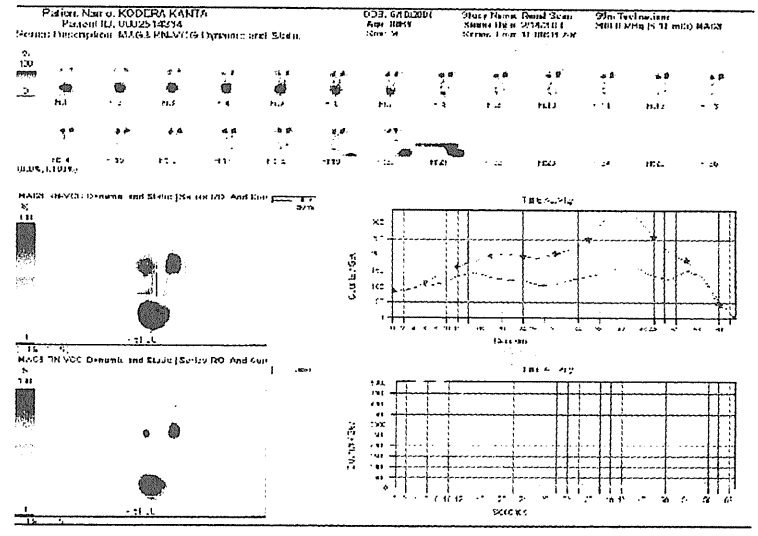


図3　排泄性尿道膀胱造影（VCUG）
右Ⅳ度，左Ⅲ度のVURあり。明らかな後部尿道弁を認めず。





	left	right
Peak time	3.5 min	4.0 min
T1/2	11.7 min	17.9 min
% uptake	14.7%	4.3%
ERPF	149 ml	43.8 ml
Pattern	N type	M2 type

図4　MAG３シンチグラフィー（６歳時）
右腎は機能低下型。間接型 VCG で両側性の VUR を認める。

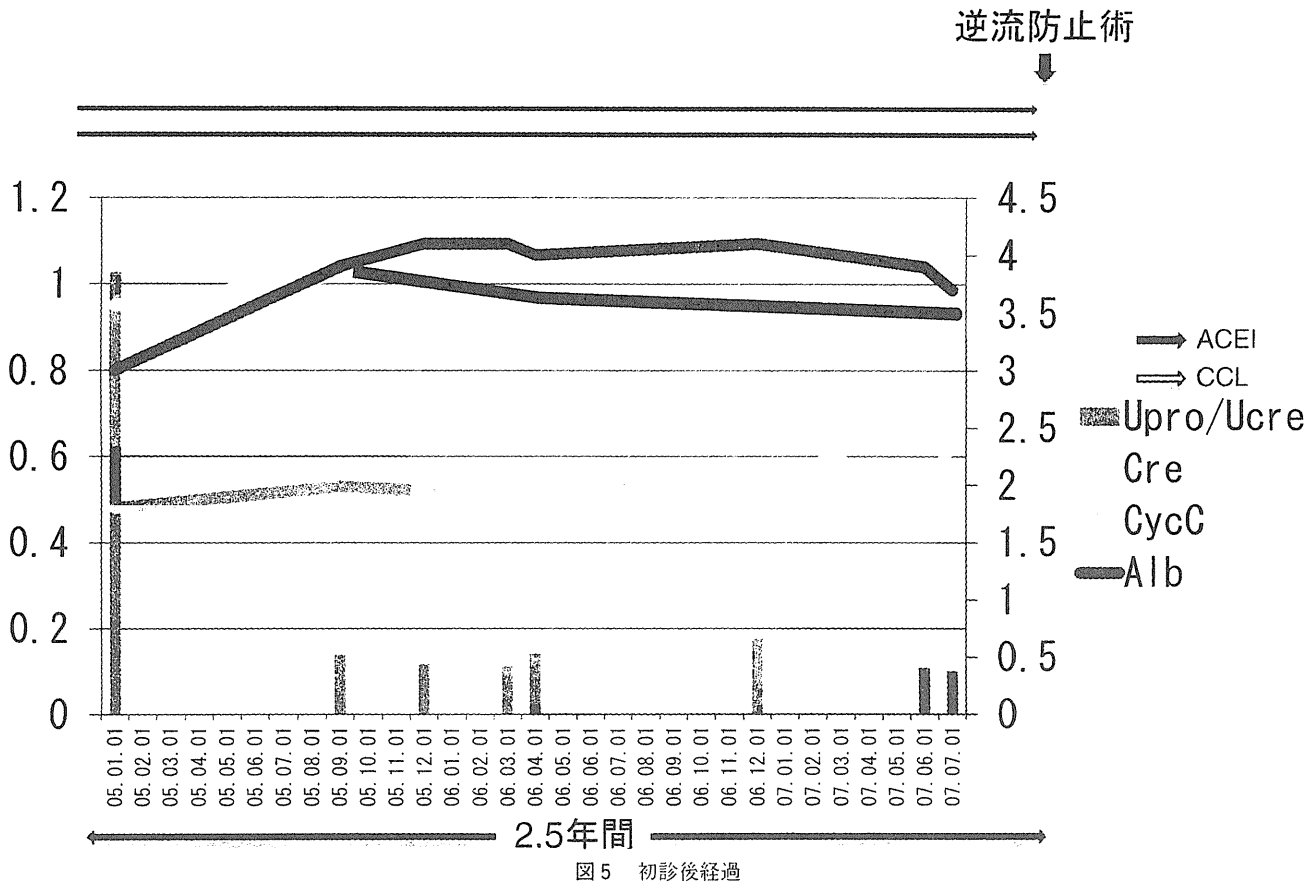


図5　初診後経過

結　語

３歳児尿検査を契機に逆流性腎症と診断した症例を経験した。小児において，非腎炎性の腎機能障害を認めた場合には画像検査が非常に有用であることがある。また，逆流性腎症の場合，一般的には VUR を治療してもその予後を変えることはできないと考えられるが，症例によっては適切なタイミングでの治療介入が有効となる可能性がある。

Eur J Pediatr (2012) 171:1401–1404
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SHORT COMMUNICATION

Is the new Schwartz equation derived from serum creatinine and body length suitable for evaluation of renal function in Japanese children?

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Abstract The present study was performed to determine whether the new Schwartz "bedside" equation can be used to estimate the glomerular filtration rate (GFR) in Japanese children as there are differences in renal function and muscle mass between Japanese and American individuals. It is also important to determine whether one common equation can be used in children from 1 to 16 years old, including the period of adolescence. Blood samples were collected from a total of 1,074 healthy children (466 males and 608 females) between 1 and 16 years old. The estimated GFR (eGFR) derived by the new Schwartz bedside formula [eGFR (in milliliters per minute per 1.73 m^2)=0.413×body length (in centimeters)/serum Cr value (in milligrams per deciliter)] was calculated in all subjects, and the relationship between age and eGFR was analyzed. The eGFR decreased gradually with age, and the decrease was more marked in males than females, mainly in adolescence. Weak negative but significant correlations were observed in 466 males and 608 females. The median of the eGFR value showed a gradual significant decrease with age. Conclusion: A common coefficient cannot be used in children between 1 and 16 years old, including the period of adolescence, with the Schwartz type formula, and the new Schwartz bedside formula cannot be used when we estimated GFR in Japanese children. It is necessary to establish an eGFR equation specifically for Japanese children.

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Keywords Reference serum creatinine level · Japanese children · Enzymatic method · New Schwartz formula · eGFR

Introduction

Schwartz et al. expressed the relations between body length, glomerular filtration rate (GFR), and serum Cr level as estimated GFR [eGFR (in milliliters per minute per 1.73 m^2)=κ×body length (in centimeters)/serum Cr value (in milligrams per deciliters)] [2]. The coefficient κ is 0.33 in preterm infants under 1 year old, 0.45 in full-term infants under 1 year old, 0.55 in children 2–12 years old, and 0.55 and 0.70 in females and males over 12 years old, respectively [2–5]. This formula is clinically useful as it allows estimation of the patient's GFR from body length and serum Cr level. This equation utilizes the Jaffe method to measure Cr. However, enzymatic methods have recently been used to measure Cr, making the above formula no longer applicable. In 2009, the updated Schwartz formula, the so-called bedside version, was reported as follows: eGFR (in milliliters per minute per 1.73 m^2)=0.413×body length (in centimeters)/serum Cr value (in milligrams per deciliter) by enzymatic Cr determination in children 1–16 years old [6].

We have previously reported reference serum creatinine levels determined by an enzymatic method in Japanese children according to sex and age [7]. The present study was performed to determine whether the new Schwartz "bedside" equation can be used to estimate the GFR in Japanese children as there are differences in renal function and muscle mass between Japanese and American individuals. It is also important to determine whether one common

equation can be used in children from 1 to 16 years old, including the period of adolescence.

Materials and methods

Blood samples were collected from a total of 1,151 children (517 males, 634 females) between 1 month and 18 years old presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease (CKD) and Tokyo Health Service Association between 2008 and 2009 without renal, urogenital, infectious, inflammatory, muscular, cardiovascular, liver, and pancreas diseases and not being hypertensive, dehydrated, or pregnant [7]. The study was approved by the local ethics boards of all participating institutions, and written informed consent was obtained from the parents of all subjects. Data from children under 1 or over 16 years old were excluded, and the remaining data from 1,074 children (466 males, 608 females) between the ages of 1 and 16 years were used in this study.

Subjects were divided into the following groups based on age. The eGFR derived by the new Schwartz formula [eGFR (in milliliters per minute per 1.73 m^2)=0.413×body length (in centimeters)/serum Cr value (in milligrams per deciliter)] was calculated in all subjects and the median, 2.5 percentile, and 97.5 percentile values of the eGFR in each age and sex. In all subjects, the relationship between age and eGFR was determined by linear regression analysis.

Serum samples were stored at −70 °C until serum Cr was measured at SRL, Inc. (Tokyo, Japan). The serum level of Cr was determined by an enzymatic method using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Ltd., Tokyo, Japan) with Pureauto S CRE-L (Sekisui Medical Co., Ltd., Tokyo, Japan). The coefficient of variation was satisfactory (2.08 %).

All analyses were conducted using Microsoft Excel 2007 (Microsoft, Redmond, WA) and the statistical software package JMP 8 (SAS Institute Inc, Cary, NC). We conducted linear regression analysis to determine whether the new Schwartz formula can be used to evaluate the renal function in Japanese children. We used Wilcoxon's analysis to compare differences in the reference eGFR values between the ages. In all analyses, $P<0.01$ was taken to indicate statistical significance.

Results

We examined the correlations between eGFR derived by new Schwartz formula and age in males and females (Fig. 1). These scattergrams showed that eGFR decreased gradually with age, and the decrease was more marked in males than females mainly in adolescence. Weak correlations were

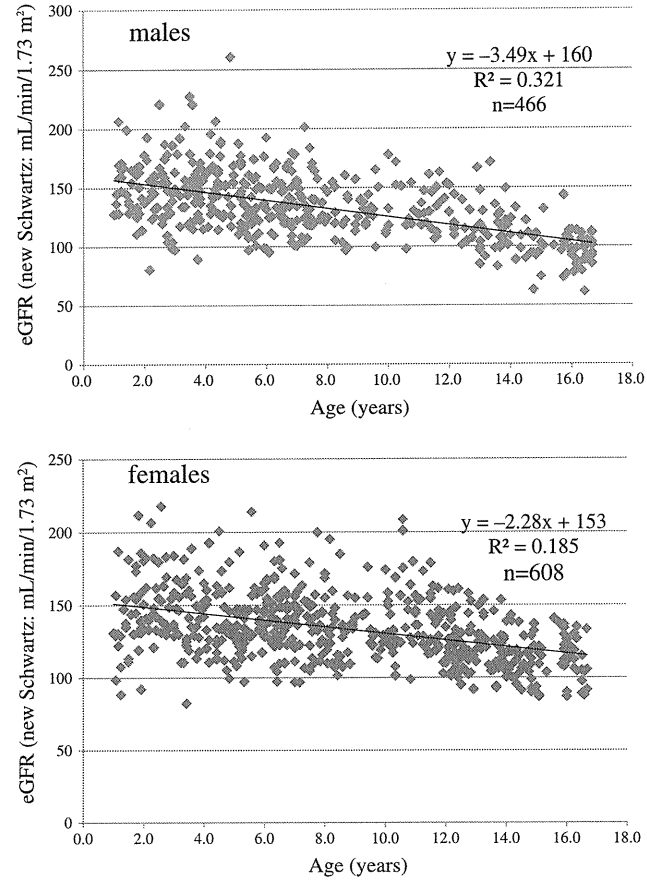

Fig. 1 Correlation between eGFR derived by the new Schwartz bedside formula and age in all male and female subjects, respectively. The scattergram shows that eGFR decreased gradually with age showing a weak but significant negative correlation

observed in 466 males and 608 females, and the correlation coefficients were 0.567 and 0.430 (Fig. 1, $P<0.001$), respectively.

We reviewed the median, 2.5 percentile, and 97.5 percentile of the eGFR value in each age group between 1 and 16 years old in males and females, respectively (Table 1). The median of the eGFR value decreased gradually with age, i.e., 130–150 mL/min/1.73 m^2 between 1 and 11 years old and 95.9 mL/min/1.73 m^2 in males and 112.3 mL/min/1.73 m^2 in females at 16 years old, respectively ($P<0.001$).

Discussion

GFR is used to assess kidney function and is measured by renal clearance. Inulin clearance is the gold standard for evaluation of kidney function but cannot be measured easily. Therefore, various methods have been used to determine GFR. The eGFR (in milliliters per minute per 1.73 m^2)=κ× body length (in centimeters)/serum Cr value (in milligrams per deciliter) by the Jaffe method devised by Schwartz has been used clinically [2]. Recently, however, enzymatic

Table 1 The median, 2.5 percentile, and 97.5 percentile of the eGFR value in each age group between 1 and 16 years old in males and females, respectively

Age (years old)	*n*	2.5 %	50 %	97.5 %
Males				
1	33	113.3	147.5	200.7
2	40	98.0	146.2	193.4
3	48	100.2	148.7	217.6
4	43	116.9	149.6	206.0
5	47	99.2	134.8	177.2
6	43	98.2	134.5	179.7
7	38	103.6	131.4	185.0
8	18	97.8	123.4	159.1
9	18	104.5	130.6	159.0
10	12	103.5	131.3	176.0
11	19	106.9	133.8	162.3
12	15	102.4	116.0	161.4
13	30	84.3	112.5	155.4
14	17	73.1	98.0	129.1
15	15	73.8	103.0	139.2
16	30	73.3	95.9	113.2
Females				
1	36	91.8	136.4	190.1
2	33	128.1	148.7	208.8
3	40	109.8	140.8	184.2
4	38	104.9	136.2	193.4
5	49	108.8	132.7	181.7
6	58	105.4	140.3	186.8
7	47	98.1	137.6	178.1
8	38	106.8	132.7	185.9
9	17	113.5	129.2	167.8
10	32	100.9	132.4	202.7
11	39	110.0	136.9	173.6
12	54	96.6	119.5	160.4
13	38	93.7	121.5	153.5
14	40	91.3	112.3	139.1
15	22	87.3	117.7	138.9
16	27	87.5	112.3	133.9

methods have been used to measure Cr rather than the Jaffe method, so it is not possible to use the formula in this form. Therefore, it was necessary to reevaluate the value of the coefficient κ in the formula. Recently, Zappitelli et al. revised the Schwartz formula relating eGFR to serum creatinine level determined enzymatically and reported that the κ value in the Schwartz equation decreased from 0.55 to 0.47 for children and adolescent girls [8]. Schwartz et al. reported the updated formula, the so-called bedside version, as eGFR=0.413× body length (in centimeters)/serum Cr value (in milligrams per deciliter) by the enzymatic method showing a 25 % reduction in κ value from the previous value of 0.55 generated from Jaffe-based serum Cr measurements [6]. The work was defined from a population of American children with chronic kidney disease, enriched with obstructive uropathy. They concluded that the formula can be used regardless of age or gender in children 1–16 years old. However, the work has been misread and misused to assess eGFR in healthy children.

The present study was performed to determine whether the new Schwartz bedside equation can be used for the evaluation of renal function in Japanese children. Previously, we reported reference serum creatinine levels determined by an enzymatic method in Japanese children according to sex and age [7]. The eGFR derived by the new Schwartz formula [eGFR (in milliliters per minute per 1.73 m^2)= 0.413×body length (in centimeters)/serum Cr value (in milligrams per deciliter)] was calculated for our 1,074 subjects between the ages of 1 and 16 years old and the median, 2.5 percentile, and 97.5 percentile values of the eGFR in each age and sex. The median of the eGFR value showed a gradual significant decrease with age. In addition, the relationship between age and eGFR was determined by linear regression analysis, and weak but significant negative correlations were observed in both male and female subjects. It seems to be a large problem that the ranges of the reference value of boys over 12 years and girls over 14 years old overlap a range of CKD stage 2. In healthy children, normal serum creatinine values are sufficient to define normal kidney function.

Brodehl et al. reported that GFRs derived from inulin clearance approached adult levels within 2 years and were approximately constant between 3 and 15 years old, showing values of 111.2 and 117.2 mL/min/1.73 m^2 at 3–4 years and 13–15 years old, respectively [1]. Our results indicating that eGFR value derived by the new bedside Schwartz formula decreased gradually with age suggest that this formula should not be used for estimating the GFR of Japanese children, at least in those with normal renal function. Weak points of our study are that our materials were healthy not chronic kidney disease children and that they were not actually measured with GFR. In addition, we entrusted the judgment of each coauthor whether each case met our exclusion criteria. We will go ahead through the study of the inulin clearance for patients with Japanese pediatric CKD and intend to review new Schwartz formula in this study.

Schwartz et al. expressed the relationship between body length, GFR, and serum Cr level as eGFR (in milliliters per minute per 1.73 m^2)=κ×body length (in centimeters)/serum Cr value (in milligrams per deciliter) [2], and in this old Schwartz formula, the coefficient κ is 0.55 in children 2–12 years old and 0.70 in males over 12 years old [2, 4]. The new Schwartz formula has an inherent problem with using the same coefficient between the ages of 1 and 16 years old. In addition,

we assume that renal function and muscle mass show ethnic differences.

While indeed it is inappropriate to use the new Schwartz bedside formula in normal Japanese children, it may be inappropriate in all normal children of any ancestry, ethnicity, or national origin. We must realize that it was not defined for these populations of normal children.

In conclusion, the common coefficient cannot be used between 1 and 16 years old, including the adolescent period, in the Schwartz type formula, and the new Schwartz bedside formula cannot be used when we estimated GFR in Japanese children. It is necessary to establish a specialized estimated GFR equation for use in Japanese children and to review new Schwartz formula for patients with pediatric CKD.

References

1. Brodehl J, Gellissen K, Weber HP (1982) Postnatal development of tubular phosphate reabsorption. Clin Nephrol 17:163–171
2. Schwartz GJ, Brion LP, Spitzer A (1987) The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin N Am 34:571–590
3. Schwartz GJ, Feld LG, Langford DJ (1984) A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr 104:849–854
4. Schwartz GJ, Gauthier B (1985) A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr 106:522–526
5. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
6. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637
7. Uemura O, Honda M, Matsuyama T, Ishikura K, Hataya H, Yata N, Nagai T, Ikezumi Y, Fujita N, Ito S, Iijima K, Kitagawa T (2011) Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study. Clin Exp Nephrol 15:694–699
8. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, Bell L (2006) Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis 48:221–230

Clin Exp Nephrol (2013) 17:99–105
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ORIGINAL ARTICLE

Establishment of a normal reference value for serum β2 microglobulin in Japanese children: reevaluation of its clinical usefulness

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Abstract
Objective Serum β2 microglobulin (β2MG) is considered to be a marker of renal function, which is independently associated with age. However, only a few studies have reported the reference values for β2MG in children thus far, particularly in young children. In this study, we evaluated the distribution of serum β2MG values in healthy Japanese children and assessed its clinical usefulness.
Method The normal reference value of serum β2MG was assessed in serum samples from 1131 normal Japanese children (504 boys and 627 girls; age 0–17 years). To test the validity of the reference value, serum samples from children with various kidney diseases were also examined retrospectively.
Results The mean values for β2MG were significantly negatively correlated with age ($r = -0.47$, $P < 0.001$). No significant difference was observed between the values of boys and girls in any age group. The established β2MG reference range covered 99.7 % of patients with decreased kidney function below 75 % based on their serum creatinine (Cr) value and body length.
Conclusion The newly established β2MG reference value in children can be used to detect kidney impairment in children. Serum β2MG in combination with serum Cr used as markers for predicting glomerular function can provide an accurate detection of kidney dysfunction in children.

Keywords β2 microglobulin · Body mass · Children · Chronic kidney disease · Kidney function · Reference value

Introduction

The worldwide increase in the number of patients with chronic kidney disease (CKD) is being recognized as a global public health problem. CKD is not only a cause of end-stage renal disease (ESRD) during childhood but also a key cause of CKD and ESRD in adults. Therefore, the early detection of impaired glomerular function in children, facilitated by routine examinations of kidney function, is essential to inhibit the progression of CKD and reduce the incidence of ESRD. However, this assessment is limited by the lack of markers for impaired kidney function in children. In addition, there are few studies that have established race-based reference values for children.

A multicenter study was recently conducted to establish normal reference values for serum creatinine (Cr), beta 2 microglobulin (β2MG), and cystatin C levels in Japanese children, and a normal serum Cr reference value was established for Japanese children by using an enzymatic detection method [1]. There is a significant correlation between the serum Cr concentration and body length (BL), expressed as BL (m) × 0.30 for children aged 1–12 years, providing a simple formula convenient for estimating glomerular function. A polynomial equation that can predict serum Cr values in children of all ages was also established [1]. Serum Cr is the most widely used marker

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for predicting kidney function. The newly established Cr value for Japanese children will further improve the diagnostic accuracy for detecting reduced renal function. However, Cr concentrations are insensitive to mild reduction in the glomerular filtration rate (GFR). In addition, the age and muscle mass dependencies of serum Cr complicate GFR assessment in children; physicians, particularly if they are not nephrologists or pediatricians, often do not take these complications into account [2, 3]. Therefore, additional markers independent of age and sex are preferable to aid the screening of renal function.

β2MG is a well-established marker that is independent of muscle mass and age; therefore, it has better diagnostic sensitivity than serum Cr for the detection of impaired GFR in growing children and children associated with severe loss of body mass [4, 5]. The production of β2MG, however, is known to increase during infection, inflammatory processes, proliferative syndromes, autoimmune diseases, and malignancies [6], which may affect the evaluation of glomerular function in children. Therefore, it is necessary to establish an accurate range of β2MG in healthy children, which can be used as an accurate diagnostic marker of renal dysfunction in children.

Despite the clinical importance of evaluating the renal function independent of age, sex, and race, there are few studies on normal β2MG reference values in children. Therefore, this large-scale study was performed to evaluate the normal reference values of β2MG in healthy Japanese children.

Materials and methods

Collection of blood samples (multicenter study)

Blood samples were collected from a total of 1151 children (517 boys and 634 girls) between the ages of 1 month and 18 years who presented at the member facilities of the Committee of Measures for Pediatric CKD and the Tokyo Health Service Association between 2008 and 2009 [1]. The study was approved by the local ethics boards, and written consent was obtained from the parents of all subjects. Data lacking β2MG values were deleted, and the remaining data from 1131 healthy children (504 boys and 627 girls) with ages between 1 month and 17 years (mean overall age, 7.7 ± 4.7 years; mean age of boys, 7.0 ± 4.8 years; mean age of girls, 8.4 ± 4.6 years) were used in this study. Children with kidney diseases, urogenital diseases, infectious diseases, inflammatory diseases, dehydration, muscular diseases, anomaly syndrome, malignancies, cardiovascular diseases, and liver or pancreas diseases were excluded from this study.

Measurement of B2MG

The serum samples were stored at −70 °C until further measurements were performed at SRL Inc. (Tokyo, Japan). The serum concentrations of both β2MG and Cr were determined by a latex agglutination immunoassay and an enzymatic method, respectively, by using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Ltd, Tokyo, Japan).

Test validity of reference value

The archival serum β2MG and Cr data collected from patients with various kidney diseases hospitalized between 2004 and January 2010 for routine examinations for clinical management were used to test the validity of the established β2MG reference values. The collected data included 345 serum samples from 21 children with various kidney diseases, including hypoplastic or dysplastic kidney ($n = 8$), kidney injury during the neonatal period ($n = 3$), reflux nephropathy ($n = 1$), post-hemolytic uremic syndrome ($n = 1$), focal segmental glomerulosclerosis (FSGS) ($n = 4$), congenital nephrotic syndrome ($n = 1$), IgA nephropathy ($n = 1$), drug-induced renal dysfunction ($n = 1$), and mitochondrial disease ($n = 1$). The patients were aged 0.1–13.6 years (mean 6.0 ± 4.8 years) at the time of diagnosis, and all developed decreased GFR during their disease course. Samples were collected when the patients were 0.6–16.9 years of age (mean 8.3 ± 5.3 years). The mean observation period was 3.1 ± 2.6 years. The male-to-female ratio was 14:7. All samples were confirmed to be C-reactive protein-negative to exclude the possible effect of inflammation on β2MG values. Medical records for the BL and body weight taken during blood tests were also collected. All patients gave their informed consent at the beginning of treatment for the use of the data in addition to that required for diagnostic purposes, i.e., for research purposes.

Individual serum Cr values and the reference value calculated by the recently established polynomial equation formula were used to evaluate the kidney dysfunction, as follows [1]:

$$\text{For boys: } y = -1.259x^5 + 7.815x^4 - 18.57x^3 + 21.39x^2 - 11.71x + 2.628$$

$$\text{For girls: } y = -4.536x^5 + 27.16x^4 - 63.47x^3 + 72.43x^2 - 40.06x + 8.778,$$

where y is the reference serum creatinine (mg/dl) and x is body length (m).

Thus, kidney function was defined as [patient Cr/reference Cr (y) × 100 (%)].

Statistical analysis

The statistical analysis was performed with the GraphPad Prism software package (Ver. 5.0; GraphPad Software, San Diego, CA). The reference cohort with β2MG and Cr was subdivided into separate age groups for girls and boys. The differences between the groups were tested with the Kruskal-Wallis nonparametric analysis of variance (ANOVA), Mann-Whitney *U* test, or chi-square analyses as appropriate. The relationship between age and serum β2MG concentration was determined by both linear and polynomial regression analyses. The data are expressed as the mean ± standard deviation (SD) or 95 % confidence interval (CI). Associations between age, BL, serum Cr, and kidney function (%) were assessed with correlation coefficients according to Pearson (*r*). $P < 0.05$ was defined as statistically significant in all analyses.

Results

β2MG reference values in Japanese children

The characteristics of healthy children were as follows: the mean age was 7.8 ± 4.7 years (95 % CI 7.5–8.1 years) with a range of 0.1–16.7 years and a median of 6.9 years. The mean BL was 1.21 ± 0.30 m (range 0.54–1.85 m). There were 64 children who were taking cold medicine or antiallergic agents, though no one had fever or any other symptoms of inflammation. The median, 2.5 percentile, and 97.5 percentile serum β2MG reference values in each subgroup of age are summarized in Table 1. Combining these values as a single cohort yielded a mean serum β2MG concentration of 1.45 ± 0.3 mg/l (95 % CI 1.43–1.47 mg/l). There were no differences in β2MG concentrations between boys and girls of any age group; however, the β2MG data varied widely, particularly in younger subjects (Table 1). It appears that there was a significant change in the value of the upper limit (97.5th percentile) between children aged between 1 and 2 years (Table 1).

Scattergrams show the age-dependent distribution of serum β2MG concentrations (Fig. 1) in which the serum β2MG concentration gradually decreases with age. There is a significant negative correlation among the serum β2MG concentration, age, and BL (both $r = -0.47$, $P < 0.0001$), and the regression equations were $y = -0.0341x + 1.72$ and $y = -0.0055x + 2.12$, respectively (Fig. 1a, b). The relationships between serum β2MG level and age (years) or BL (m) were also determined by polynomial regression analysis, and the reference serum β2MG level was expressed as a cubic equation of age or BL (Fig. 1a, b; broken lines). The regression equations were as follows:

Table 1 Median, 2.5th percentile, and 97.5th percentile of serum β2MG reference values in each age group according to sex

Age	All subjects				Boys				Girls			
	n	2.5 %	50 %	97.5 %	*n*	2.5 %	50 %	97.5 %	*n*	2.5 %	50 %	97.5 %
3–5 months	21	1.5	1.8[a]	3.2	17	1.5	1.8	3.2	4	1.6	1.8	2.1
6–8 months	18	1.4	1.8[a]	2.6	14	1.4	1.9	2.6	4	1.6	1.6	2.3
9–11 months	29	1.3	1.7[a]	3.3	15	1.3	1.7	3.3	14	1.3	1.8	3.2
1 years	69	1.4	1.7[a]	3.1	32	1.4	1.7	3.2	37	1.2	1.6	3.0
2 years	73	1.0	1.5	2.5	40	1.0	1.5	2.2	33	1.0	1.5	3.4
3 years	85	1.0	1.5	2.3	46	1.1	1.5	2.3	39	1.0	1.5	2.4
4 years	78	1.1	1.4	2.5	42	1.0	1.4	2.1	36	1.1	1.4	3.1
5 years	94	1.1	1.4	2.3	46	1.1	1.5	2.7	48	1.0	1.4	2.2
6 years	101	1.1	1.4	2.3	43	1.1	1.4	2.4	58	1.0	1.5	2.3
7 years	83	1.0	1.4	2.1	36	0.9	1.3	2.1	47	1.0	1.4	2.2
8 years	55	1.0	1.4	2.5	19	1.0	1.4	1.8	36	1.0	1.4	2.3
9 years	37	1.0	1.4	2.1	18	1.1	1.4	1.8	19	1.0	1.4	2.1
10 years	42	0.9	1.3	1.9	11	1.1	1.4	1.6	31	0.9	1.3	1.9
11 years	58	1.0	1.3	2.3	19	1.1	1.3	2.1	39	1.0	1.2	2.4
12 years	69	1.0	1.3	1.8	14	1.2	1.3	1.5	55	0.9	1.3	1.9
13 years	68	1.0	1.3	1.8	30	1.0	1.4	2.0	38	1.0	1.2	1.5
14 years	57	0.9	1.3	2.0	17	1.1	1.4	2.0	40	0.9	1.2	1.7
15 years	35	0.8	1.2	1.8	15	0.8	1.2	1.8	20	0.8	1.1	1.7
16 years	59	0.8	1.2	1.8	30	0.8	1.2	1.8	29	0.8	1.1	1.4
All ages	1311	1.0	1.4	2.3	504	1.0	1.4	2.3	627	1.0	1.4	2.3

[a] $P < 0.0001$ in comparison to the mean value in all subjects

For age: $y = -0.000472x^3 + 0.0139x^2 - 0.149x + 1.94$

For BL: $y = -0.354x^3 + 1.79x^2 - 3.26x + 3.36$

β2MG exhibited significant correlations with age (correlation coefficient of −0.50) and with BL (correlation coefficient of −0.49), which were slightly improved compared to those in the linear regression analysis.

There was no relationship between the β2MG concentration and age in children less than 2 years of age; however, β2MG levels showed a significant negative correlation with age in children more than 2 years of age (Fig. 1c, d). Statistical analyses revealed that the β2MG levels in age groups of 0–5 months (1.94 ± 0.44 mg/l), 6–8 months (1.92 ± 0.38 mg/l), 9–11 months (1.80 ± 0.48 mg/l), and 1 year (1.80 ± 0.42 mg/l) were significantly higher than the overall mean value of all the subjects (1.45 ± 0.34 mg/l, $P < 0.001$). However, no difference was found in the >2 years age group.

There were 14 outliers of the upper limit of age-specific values (Fig. 2a); however, these were unrelated to the corresponding Cr values, which were within the normal range (Fig. 2b). Out of the 14 children, 6 were taking cold medicine or antiallergic agents, and the number of subjects taking such medicines was significantly high (66 cases) among the total subjects ($P < 0.001$, by the chi-square test).

Assessment of β2MG value in children with CKD

The validity of the reference range of the established reference value for β2MG was tested by reviewing data from children with various kidney diseases during the course of

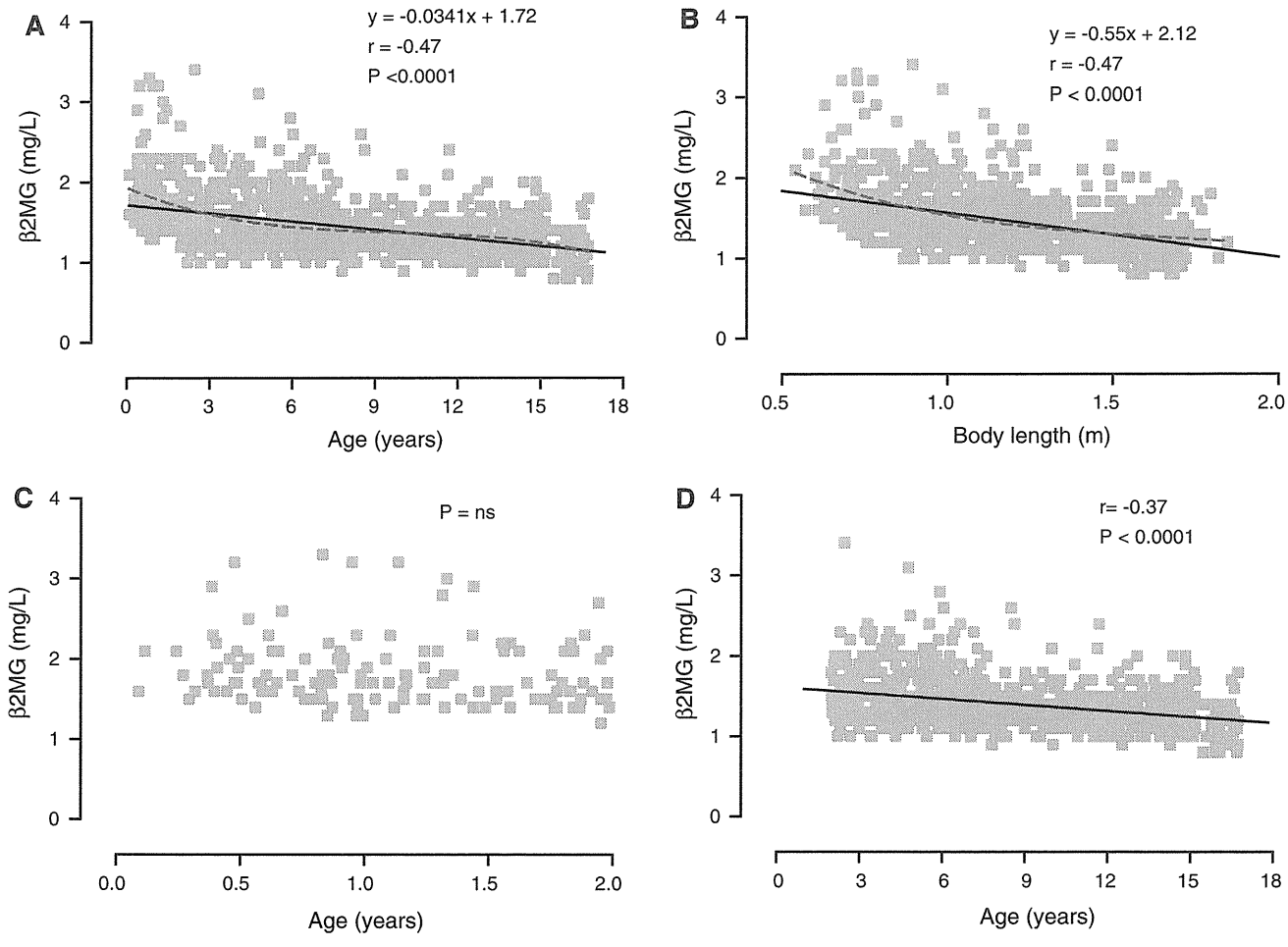

Fig. 1 Serum concentrations of β2MG in relation to age and body length (BL). Linear regression lines between the serum concentration β2MG and age (year) (**a**) or BL (m) (**b**) of all subjects are shown. The regression equations are $y = -0.0341x + 1.72$ and $y = -0.0055x + 2.12$, respectively (*straight lines*). The relationships are also determined by polynomial regression analysis, and the reference serum β2MG level is expressed as a cubic equation of age (**a**) or BL (**b**) (*broken lines*). The regression equations are as follows: $y = -0.000472x^3 + 0.0139x^2 - 0.149x + 1.94$ for age and $y = -0.354x^3 + 1.79x^2 - 3.26x + 3.36$ for BL. β2MG did not correlate with ages less than 2 years (**c**), but it did correlate significantly with ages above 2 years (**d**)

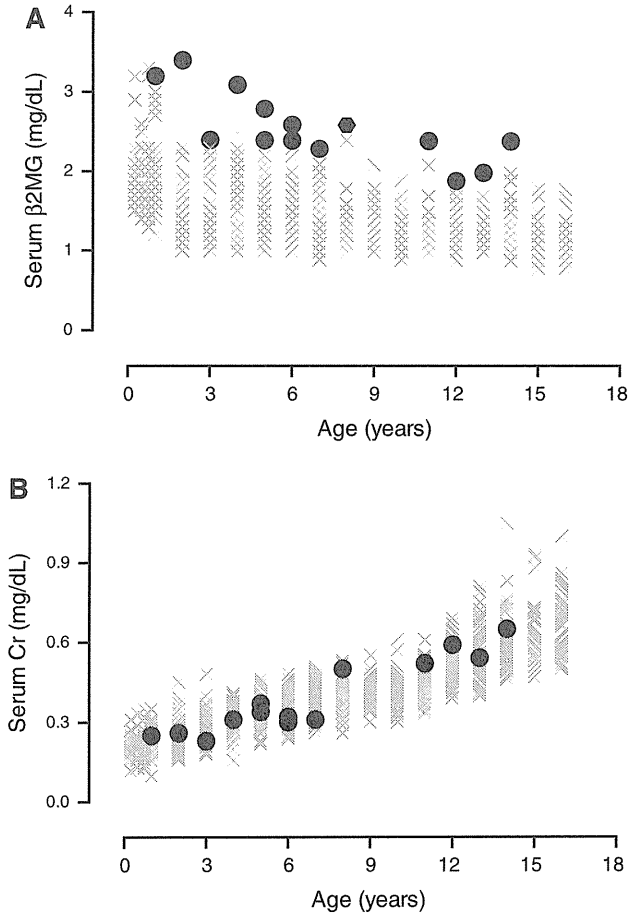

Fig. 2 Age-specific serum concentrations of β2MG (**a**) and Cr (**b**). Outliers beyond the 97.5th percentile range for β2MG reference values (**a**) and their corresponding Cr values (**b**) are shown as *black dots*

their disease. Most of the serum concentrations of β2MG were beyond the upper 97.5th percentile of age-appropriate reference values when the Cr level was beyond the 97.5th percentile of age-appropriate reference values. Out of the 345 samples, 329 indicated reduced kidney function below 75 %, and 344 of these (99.7 %) could be detected using the newly established age-specific β2MG reference range. However, data from 2 patients showed a discrepancy between the serum β2MG concentrations and serum Cr level or kidney function (Fig. 3). Their kidney function as evaluated based on the serum Cr value and BL was gradually decreased from the normal level to below 75 % during their course, but it was accompanied by a relatively quick increase of β2MG for their age (Fig. 3).

Patient 1 was a 14-year-old boy and was referred to the department of pediatric nephrology for proteinuria and severe emaciation. He had been diagnosed with mitochondrial disease by a muscle biopsy when he was 11 years old. His body weight was 21.1 kg (−3.0 SD for mean Japanese weight at his age) and body length was 136.5 cm (−3.6 SD). Laboratory data showed proteinuria, 120 mg/dl without kidney insufficiency; serum Cr, 0.42 mg/dl; and β2MG, 1.6 mg/l. His BL gradually increased to 143.8 cm (−4.4 SD) over the next 2 years, but his body weight was stable at 20 kg (−3.9 SD). The serum β2MG level gradually increased with the decrease of kidney function and exceeded the upper limit (97.5th percentile) of the established standard range for his age when he was 15.6 years old (Fig. 3a). At that time, an endogenous Cr clearance (CCr) test revealed his CCr to be 53.0 ml/min/1.73 m^2.

Patient 2 was a boy diagnosed with FSGS when he was 13 years old. At diagnosis, his serum Cr and β2MG levels were 0.5 mg/dl and 1.9 mg/l, respectively. His BL was 144.6 cm (−1.6 SD for the mean Japanese BL at his age) and calculated kidney function was 110.3 %. In addition to FSGS, he had an uncontrolled nephrotic range of proteinuria, and his kidney function decreased below 75 % in the next 9 months (Fig. 3b). His serum levels of both Cr and β2MG were elevated according to his kidney function, and the β2MG level was beyond the upper 97.5th percentile range during the same time that the kidney function decreased below 75 %. In contrast, his serum Cr level was still within the normal range for his age when the calculated kidney function decreased below 75 % (Fig. 3b).

Discussion

Several serum markers, including Cr, β2MG, and cystatin C, have been used to evaluate kidney function [7, 8]. However, for the use of these markers in children, an understanding of their normal reference values and their relationships with age and build according to differences among races is essential. Therefore, we recently conducted an ongoing multicenter large-scale study to examine this point. The reference value for serum Cr in healthy Japanese children has already been established [1]. The present study was aimed at determining the reference range of β2MG in healthy Japanese children as the second step of our study.

In this study, we found a significant correlation between β2MG concentration and age (Fig. 1a), which was different from previous reports [4, 5]. There was also a significant negative correlation between β2MG and BL, and they had the same regression coefficient ($r = -0.47$) (Fig. 1b). Therefore, it can be argued that the independent relation of β2MG with age and body mass, which has been one of the advantages for its use as a marker, is not applicable in studies on children. However, the current study showed that the slope of the regression line for β2MG with age is gradual and reaches a plateau in a short time (Fig. 1). Moreover, β2MG and age are negatively correlated, and therefore, elevations in β2MG concentrations relative to age can be easily detected. Indeed, the retrospective

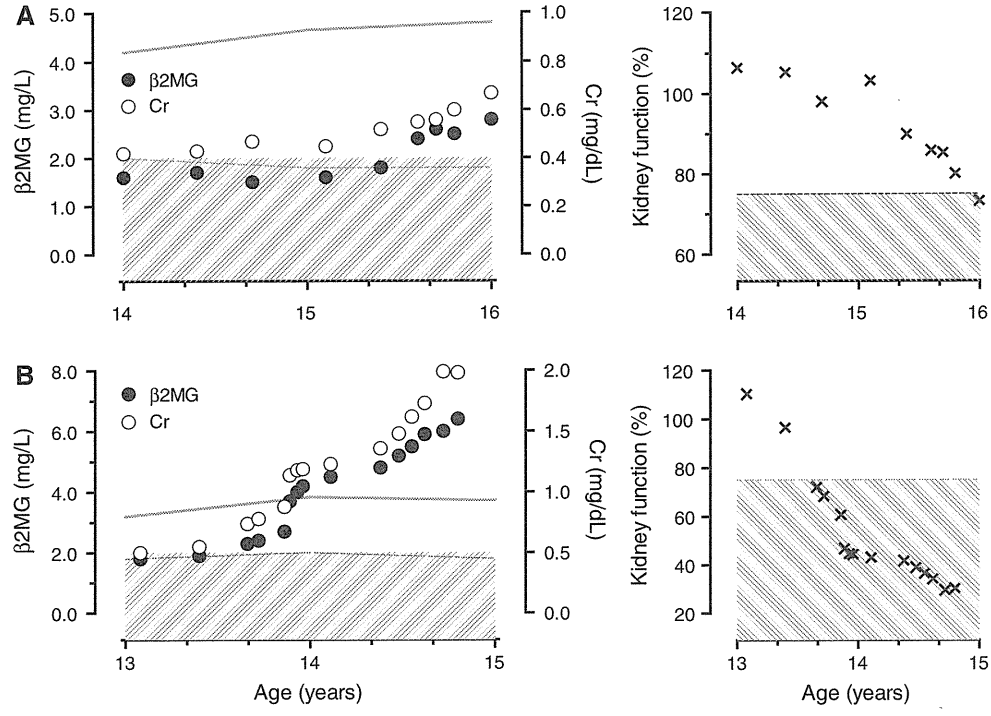

Fig. 3 Time course of kidney function (%) and serum β2MG and Cr concentrations in patient 1 (**a**) and patient 2 (**b**). *Shaded area* and *solid line in the left panel* represent the age-specific reference range (2.5–97.5th percentile) for β2MG and Cr, respectively. The *shaded area in the right panel* represents the age-specific reference range for kidney function under 75 %

assessments tested the clinical validity of the newly established β2MG reference in patients with various kidney diseases, distributed over a wide range of age groups, revealed that β2MG was a highly sensitive marker (99.7 %) for detecting kidney dysfunction below 75 %.

β2MG forms the beta chain of the human leukocyte antigen class I molecule and is present on the surface of most nucleated cells [9]. Although the mechanism of the dependency of β2MG on age is unknown, many immunological features in children, including an immature immune system in infants and lymphocytic predominance of circulating leukocytes in young children, could explain how serum β2MG concentrations change with age. Many of the subjects among the high β2MG outliers were taking cold medicine or antiallergic agents, indicating that some kind of immune reaction caused by the common cold or some allergic diseases, including bronchial asthma and atopic dermatitis, could affect β2MG production. Indeed, such diseases are common among young children. Data from studies examining serum β2MG values in fetuses or neonates reveal that the mean value of β2MG is relatively higher (around 3.5 mg/l) than that of young children with no renal complications in the present study [10, 11].

The current study used the equation for kidney function derived from serum Cr: kidney function (%) = (reference serum Cr/patient's serum Cr) × 100, since the reciprocal of serum Cr is generally correlated with GFR [12, 13]. Assuming 100 % kidney function to be GFR 120 ml/min, 75 % kidney function is comparable to GFR 90 ml/min, which is the borderline between CKD stage 1 and 2 [14]. An advantage of using this method is that since this formula is based on BL rather than age, kidney function can be appropriately estimated for growing children. There are, however, still significant disadvantages of using Cr as a marker for detecting mild impairment of kidney function in children. Herein, we presented a typical case of this situation (Fig. 3). In children with a very low muscle mass, Cr-based estimation of GFR can be misleading. Cr can also be overestimated in children with advanced renal failure, in whom there is reduced Cr production due to malnutrition [13]. Although β2MG has the disadvantage of being increased in patients with inflammatory and infectious diseases and several malignancies [6], detection of increased β2MG concentrations appears to be easier than that of Cr. Therefore, as compared to Cr, β2MG appeared to be a better marker of kidney impairment in children with abnormally low body mass. It also appears to be favorable for children with short stature in mild kidney dysfunction.

In addition to β2MG, recent studies have reported that cystatin C also facilitates the recognition of abnormal renal function in children compared to Cr because its reference range is independent of age, gender, height, and body composition [7, 8]. The applicability of cystatin C, however, remains a matter of debate. A standard value for cystatin C in children has not yet been established; therefore, considering the diagnostic sensitivity of cystatin C for impaired GFR in pediatric patients, particularly in patients with only mildly impaired kidney function, cystatin C may not be a better indicator than the BL/Cr ratio [15]. Furthermore, the measurement of cystatin C is currently too

expensive for routine use in clinical practice. However, cystatin C will also be a potentially useful marker once a reference value in normal children, according to race, has been established, and the differences between the diagnostic significance of Cr and β2MG become clear. We believe that our ongoing large-scale study that aims to establish the reference value of cystatin C in Japanese children will provide a better understanding of this marker for clinical use.

In summary, the current study determined a new β2MG reference value for detecting kidney impairment in children. Measurement of the serum β2MG concentrations in combination with serum Cr concentrations, and perhaps cystatin C in the near future, as markers for predicting glomerular function will provide better accuracy in the detection of reduced kidney function in children.

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References

1. Uemura O, Honda M, Matsuyama T, Ishikura K, Hataya H, Yata N, Nagai T, Ikezumi Y, Fujita N, Ito S, Iijima K, Kitagawa T. Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study. Clin Exp Nephrol. 2011;15:694–9.
2. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics. 1976;58:259–63.
3. Kwong MB, Tong TK, Mickell JJ, Chan JC. Lack of evidence that formula-derived creatinine clearance approximates glomerular filtration rate in pediatric intensive care population. Clin Nephrol. 1985;24:285–8.
4. Donadio C, Lucchesi A, Ardini M, Giordani R, Cystatin C. Beta 2-microglobulin, and retinol-binding protein as indicators of glomerular filtration rate: comparison with plasma creatinine. J Pharm Biomed Anal. 2001;24:835–42.
5. Filler G, Priem F, Lepage N, Sinha P, Vollmer I, Clark H, Keely E, Matzinger M, Akbari A, Althaus H, Jung K. Beta-trace protein, cystatin C, beta(2)-microglobulin, and creatinine compared for detecting impaired glomerular filtration rates in children. Clin Chem. 2002;48:729–36.
6. Karlsson FA, Wibell L, Evrin PE. Beta 2-microglobulin in clinical medicine. Scand J Clin Lab Invest Suppl. 1980;154:27–37.
7. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C—a new marker of glomerular filtration rate in children independent of age and height. Pediatrics. 1998;101:875–81.
8. Sharma AP, Yasin A, Garg AX, Filler G. Diagnostic accuracy of cystatin C-based eGFR equations at different GFR levels in children. Clin J Am Soc Nephrol. 2011;6:1599–608.
9. Vincent C, Revillard J. B2M and HLA-related glycoproteins in human urine and serum. Contr Nephrol. 1981;26:66–88.
10. Assadi FK, John EG, Justice P, Fornell L. Beta 2-microglobulin clearance in neonates: index of tubular maturation. Kidney Int. 1985;28:153–7.
11. Engle WD, Arant BS Jr. Renal handling of beta-2-microglobulin in the human neonate. Kidney Int. 1983;24:358–63.
12. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem. 1992;38:1933–53.
13. Hari P, Bagga A, Mahajan P, Lakshmy R. Effect of malnutrition on serum creatinine and cystatin C levels. Pediatr Nephrol. 2007;22:1757–61.
14. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–266.
15. Filler G, Priem F, Vollmer I, Gellermann J, Jung K. Diagnostic sensitivity of serum cystatin for impaired glomerular filtration rate. Pediatr Nephrol. 1999;13:501–5.

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Pre-dialysis chronic kidney disease in children: results of a nationwide survey in Japan

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Abstract

Background. Chronic kidney disease (CKD) in children is a progressive and intractable condition that may severely impair the child's growth, development and quality of life. Epidemiological information on pediatric CKD, particularly in Asians, is scant.

Methods. We conducted a nationwide survey of Japanese children aged 3 months to 15 years with pre-dialysis CKD to examine the prevalence of pediatric CKD in Japan. CKD was classified according to newly established criteria derived from reference serum creatinine levels in Japanese children. Surveys were sent to 1190 institutions across Japan to report on cases of pediatric CKD managed as of 1 April 2010.

Results. A total of 925 institutions (77.7%) responded. Information on 447 children was collected. When subdivided according to our diagnostic criteria, 70.5% of children had stage 3 CKD, 23.9% stage 4 and 5.6% stage 5. The estimated prevalence of Japanese children with CKD was 2.95 cases/100 000 children. Of 407 CKD cases with non-glomerular disease, 278 (68.3%) had congenital anomalies of the kidney and urinary tract (CAKUT). The newly established criteria showed good validity compared with existing criteria, including the abbreviated Schwartz equation.

Conclusions. Findings from the first nationwide survey of pre-dialysis CKD in Asian children indicate that the prevalence of stage 3–5 CKD in children in Japan aged 3 months to 15 years is 2.95 cases/100 000 children. Most children with CKD presented with non-glomerular disease, most frequently CAKUT. Improved management of CAKUT, including renoprotective treatment and urological intervention, is required.

Keywords: adolescent; child; creatinine; epidemiology; Japan; kidney diseases; preschool

Introduction

Chronic kidney disease (CKD) in children is a progressive and intractable condition, with devastating effects on the patient's growth, development and quality of life. If left untreated, pediatric CKD eventually progresses to end-stage renal disease (ESRD), which requires long-term dialysis or repeated renal transplantation. The mortality rate for children with ESRD on dialysis is estimated to be 30–150 times that of the general pediatric population [1, 2]. Therefore, it is particularly important to detect CKD as early as possible, possibly by applying simple but accurate screening of at-risk children. Early identification of these children can then allow the physician to promptly introduce appropriate therapy that can prevent or slow the progression of CKD to ESRD, reducing the incidence of stage 5 CKD and to control comorbidity.

Epidemiological information on CKD in children is currently limited, but this sort of information is necessary to understand the extent of the problem, to identify populations at risk and to determine the efficacy of current therapeutic interventions. Although several studies have described the epidemiology of pre-dialysis CKD in children in Western countries [3–10], very few have focused on Asian children. It is also important to consider that there may be differences in the epidemiology of CKD among countries that may be due to racial differences, variations in screening methods among medical

Table 1. Diagnostic criteria for stage 3–5 chronic kidney disease based on reference serum creatinine levels (mg/dL) of Japanese children aged 3 months to 11 years

Age	2.5th percentile	50th percentile	97.5th percentile	CKD stage 3	CKD stage 4	CKD stage 5
<2 years						
3–5 months	0.14	0.20	0.26	0.41–0.80	0.81–1.60	≥1.61
6–8 months	0.14	0.22	0.31	0.43–0.84	0.85–1.68	≥1.69
9–11 months	0.14	0.22	0.34	0.47–0.92	0.93–1.84	≥1.85
1 year	0.16	0.23	0.24	0.47–0.92	0.93–1.84	≥1.85
2–12 (years)						
2	0.17	0.24	0.37	0.49–0.96	0.97–1.92	≥1.93
3	0.21	0.27	0.37	0.55–1.08	1.09–2.16	≥2.17
4	0.20	0.30	0.40	0.61–1.20	1.21–2.40	≥2.41
5	0.25	0.34	0.45	0.69–1.36	1.37–2.72	≥2.73
6	0.25	0.34	0.48	0.69–1.36	1.37–2.72	≥2.73
7	0.28	0.37	0.49	0.75–1.48	1.49–2.96	≥2.97
8	0.29	0.40	0.53	0.81–1.60	1.61–3.20	≥3.21
9	0.34	0.41	0.51	0.83–1.64	1.65–3.28	≥3.29
10	0.30	0.41	0.57	0.81–1.60	1.61–3.20	≥3.21
11	0.35	0.45	0.58	0.91–1.80	1.81–3.60	≥3.61

Values were matched for age alone. Values for the 2.5, 50 and 97.5th percentiles are as presented in Uemura *et al.* [11]. Table reproduced with the permission of the Japanese Society of Nephrology.

institutions and differences in in-school screening programs. To address this problem of limited information in Asian children and to assist subsequent population-based surveys, we previously determined reference serum creatinine (SCr) levels in Japanese children [11].

Our first objective in this study was to determine the prevalence of pre-dialysis CKD in a cross-sectional, nationwide survey of Japanese children aged 3 months to 15 years with pre-dialysis CKD. Stage 3–5 CKD was detected and classified using newly established criteria derived from normal SCr levels of age- and sex-matched Japanese children. Because CKD is defined as a GFR of <60 mL/min/1.73 m^2 (less than half of normal GFR) in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [12, 13] and the Kidney Disease: Improving Global Outcomes (KDIGO) position statement [14] (corresponding to stage 3 or worse), we focused on patients meeting this criterion and who had not yet received dialysis or renal transplantation. Our second objective was to determine the etiology of CKD as well as the method of detection of CKD and the treatment modalities used in routine clinical practice in Japan.

Materials and methods

Establishment of new diagnostic criteria for CKD in children

The new diagnostic criteria for stage 3–5 CKD were based on previously established reference SCr levels of Japanese children [11]. Briefly, in that study, body length and SCr levels were determined in 1151 healthy children aged 1 month to 18 years who presented at the facilities of the Committee of Measures for Pediatric CKD and Tokyo Health Service Association between 2008 and 2009. Reference intervals of SCr against age were calculated in children aged 3 months to 11 years, and those against age and sex were calculated in children aged 12–16 years.

According to the K/DOQI guidelines [12, 13] and KDIGO position statement [14] for CKD, stage 3–5 CKD was classified as GFR 30–59, 15–29 and <15 mL/min/1.73 m^2, respectively (<1/2, <1/4 and 1/8 of normal GFR, respectively), whereas normal GFR was considered to be ~120 mL/min/1.73 m^2. Given that the GFR is inversely proportional to SCr for a given body type and age [15], we classified stage 3–5 CKD as SCr more than twice, four times and eight times, the median normal SCr levels matched for age alone in children aged 3 months to 11 years (Table 1), or matched for age and sex in children aged 12–16 years (Table 2).

Table 2. Diagnostic criteria for stage 3–5 chronic kidney disease based on reference serum creatinine levels (mg/dL) of Japanese male and female children aged 12–15 years

	2.5th percentile	50th percentile	97.5th percentile	CKD stage 3	CKD stage 4	CKD stage 5
Males (years)						
12	0.40	0.53	0.61	1.07–2.12	2.13–4.24	≥4.25
13	0.42	0.59	0.80	1.19–2.36	2.37–4.72	≥4.73
14	0.54	0.65	0.96	1.31–2.60	2.61–5.20	≥5.21
15	0.48	0.68	0.93	1.37–2.72	2.73–5.44	≥5.45
Females (years)						
12	0.40	0.52	0.66	1.05–2.08	2.09–4.16	≥4.17
13	0.41	0.53	0.69	1.07–2.12	2.13–4.24	≥4.25
14	0.46	0.58	0.71	1.17–2.32	2.33–4.64	≥4.65
15	0.47	0.56	0.72	1.13–2.24	2.25–4.48	≥4.49

Values were matched for age and sex. Values for the 2.5, 50 and 97.5th percentiles are as presented in Uemura *et al.* [11]. Table reproduced with the permission of the Japanese Society of Nephrology

Study design and population

This was a cross-sectional, nationwide, population-based survey conducted by the Pediatric CKD Study Group in Japan in conjunction with the Committee of Measures for Pediatric CKD of the Japanese Society of Pediatric Nephrology (JSPN). Two surveys were sent in August 2010 to a total of 1190 institutions in Japan, including all institutions that are members of the JSPN, all university and children's hospitals and all general hospitals with >200 beds, inviting them to report cases of pediatric CKD that were managed as of 1 April 2010. We selected these types of hospital because children with apparent CKD were usually referred to institutions meeting one of these criteria. The deadlines for the first and second surveys were October 2010 and November 2010, respectively.

The first questionnaire was designed to record the presence and approximate number of children with stage 3–5 CKD in each institution. The second questionnaire recorded data for each case, including age, date of birth, sex, height, SCr level, primary renal diagnosis and associated diseases, method of detection, co-morbidities and prescribed