Three kidneys, two diseases, one antibody?

In the literature, two different autoantibodies have been described, suggesting different pathogenesis: the factor H C-terminal surface-binding region would be the target of aHUS autoantibodies, while ‘miniautoantibodies’ targeting the factor H N-terminal regulatory domain would be involved in MPGN [6]. The first would promote endothelial cell damage by affecting surface regulatory functions of factor H. The second scenario has been described in only one patient [3] in which IgG lambda-chain dimers would affect factor H regulatory function in the fluid phase. Our case, however, suggests that the same autoantibody will disturb factor H activity and according to the environment will result in either MPGN or aHUS.

This case underlines the need for complete exploration of complement pathway, especially in relation to the major regulator protein factor H when confronted with cases of both MPGN and aHUS. In our case, plasma exchanges finally allowed us to suppress anti-factor H antibody though this was performed too late to save the second transplant. However, in theory, plasma exchanges and rituximab therapy [7] or even the use of eculizimab (humanized plant. However, in theory, plasma exchanges and rituximab therapy [7] or even the use of eculizimab (humanized antibody) [8], before and during the second transplantation, might have blocked the development of aHUS on the second renal graft. Finally, this case supports the hypothesis that MPGN and aHUS are closely linked by common pathogenic mechanisms, with a central role for the dysregulation of the complement alternative pathway [6].

Acknowledgements. Many thanks to Stuart Fraser for English corrections.

Conflict of interest statement. None declared.

References

Received for publication: 9.5.11; Accepted in revised form: 27.6.11

Diffuse thin glomerular basement membrane in association with Fabry disease in a Chinese female patient

Zhi-yong Cai1,2,3, You-kang Zhang1,2,3, Su-xia Wang1,2,3, Qiu-yuan Fang1,2,3 and Yu-qing Chen1,2,3

1Renal Division, Department of Medicine, Peking University First Hospital, Beijing, China, 2Institute of Nephrology, Peking University, Beijing, China and 3Key Laboratory of Renal Diseases, Ministry of Health of China, Beijing, China

Correspondence and offprint requests to: Su-xia Wang; E-mail: suxiawang@bjmu.edu.cn

Abstract
We report a 41-year-old Chinese female with Fabry disease and diffuse thinning of the glomerular basement membrane (GBM). The patient presented with peripheral edema, mild proteinuria, microscopic hematuria, normal renal function, hypertension and tinnitus. Family screening showed that her daughter had microscopic hematuria, tinnitus and neuropathic pain. Renal biopsy of the proband showed focal segmental glomerulosclerosis with cytoplasmic vacuolization of the glomerular visceral epithelial cells by light microscopy. Laminated myelin inclusions in some of the glomerular podocytes, parietal epithelia, distal tubular epithelial cells and vascular endothelial cells along with diffuse thinning of the GBM (mean thickness of GBM: 216 ± 31 nm) were identified by electron microscopy. Genetic analysis detected a de novo novel GLA mutation, 1208 ins 21 bp, while a new variant of COL4A3 SNP M1209I was carried by mother and daughter as well as the proband’s father (I-1) and one sister (II-4). The coexistence of thinned GBM should be considered in patients with Fabry disease-manifested familial hematuria.

Keywords: COL4A3; Fabry disease; GLA; thin basement membrane nephropathy; mutation

© The Author 2011. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.
For Permissions, please e-mail: journals.permissions@oup.com

doi: 10.1093/ndt/gfr455
Advance Access publication 22 August 2011
Fabry disease (Anderson–Fabry disease, FD, OMIM 301500) is an X-linked inherited disorder caused by mutations of GLA gene, which encodes the α-galactosidase A (α-Gal A). The disease results in intracellular accumulation of enzyme substances, mainly globotriaosylceramide (Gb3) in the lysosomes of a variety of organs [1]. The kidneys are one of the main target organs. Fabry nephropathy manifests as proteinuria and progressive renal dysfunction [2, 3]. The homozygous males usually present the classical phenotypic of FD and develop end-stage renal disease in the third to fifth decades of life, while heterozygous females show variable clinical features [4].

Diffuse thinning of the glomerular basement membrane (GBM) is a characteristic of thin basement membrane nephropathy (TBMN), which usually presents with persistent hematuria and normal renal function. About 40% of TBMN cases have been associated with heterozygous mutations of COL4A3 and COL4A4 [5–7]. Here, we firstly report a case of FD coexisting with TBMN in a Chinese female.

Case report

A 41-year-old female was referred in 2006 for evaluation of proteinuria, intermittent swelling of the ankles and hypertension. She suffered from chronic pain in childhood, hypohidrosis, tinnitus, vertigo, and fatigue. There was no history of diabetes or macroscopic hematuria. Her blood pressure was 160/100 mmHg, pulse rate 78 beats per min and temperature 36.7°C. A few reddish angiokeratomas on the abdomen were detected. Urinalysis showed a proteinuria of 0.75 g/24 h, RBC 4–6 per HP. The serum creatinine was 0.92 mg/dL, respectively. According to the Chinese formula, her estimated glomerular filtration rate (eGFR) was 71.83 mL/min (eGFR (mL/min/1.73 m²) = 175 * (Scr, mg/dL)¹.234 * (age, year)⁻¹.0179 * (0.79 female)). Other measurements including serum complements, ANA, ANCA and hepatitis serology of HBV and HCV, were normal or negative. Shortening of the PR intervals and hypertrophy of the left ventricular wall were detected by Holter ECG and echocardiogram. Renal ultrasound identified a cyst with a diameter of 12 mm on the upper right kidney. Audiometric test showed a high-frequency loss at 8 kHz of the right ear. The examination of ophthalmology was normal.

Her 20-year-old daughter (III-1) had neuropathic pain, hypohidrosis, tinnitus, vertigo, transient ischemic attack as well as hematuria. One of her sisters (II-4) had isolated hematuria without proteinuria, hypertension, renal insufficiency or any sign of FD.

Renal biopsy of the proband revealed that 4/35 glomeruli had global sclerosis on light microscopy, 3 showed segmental sclerosis with adhesion to the capsule and the remaining showed mild mesangial expansion with cytoplasmic vacuolization of the visceral epithelial cells. Focal atrophy of tubules with mild interstitial infiltrates was observed. There was moderate arteriolar sclerosis. Collagen Type IV α3 and α5 chains were normally positive while no immune deposits were detected by immunofluorescence (IF). Electron microscopy (EM) showed laminated myelin inclusions in some of the podocytes, parietal epithelia, endothelial cells, distal tubular epithelial cells and interstitial vascular endothelial cells. Diffuse thinning of the GBM with a thickness of 216 ± 31 nm was identified (Figure 1) without splitting or lamellation. (The normal range of GBM thickness in a Chinese female is 335 ± 39 nm in our laboratory).

Enzyme activity of α-Gal A was determined in isolated blood leukocytes using a fluorometric assay [8]. Leukocyte levels of α-Gal A, respectively, were 33 and 75 u in the proband and her daughter (III-1); both were lower than the normal level (50 normal controls established the normal range was 100–500 U). Other members of her family had normal α-Gal A levels.

Genetic analysis of GLA and COL4A3, COL4A4, COL4A5 genes revealed novel variants of 1208 ins 21 bp in Exon 7 of GLA (Supplementary Figures 1, 2) and M1209I with the methionine substitution of isoleucine in Exon 42 of COL4A3 (Supplementary Figure 3), respectively, which were not reported previously. Their presentation in 50 non-hematuric healthy individuals, defined 1208 ins 21 bp of GLA as a mutation, while M1209I of COL4A3 was detected in 2% of a healthy population, as a polymorphism (Table 1).

Family screening for a GLA mutation and COL4A3 polymorphism is shown in Figure 2. The proband (II-2) and her daughter (III-1) carried the novel GLA mutation 1208 ins 21 bp and COL4A3 SNP M1209I; the proband’s father (I-1) and one sister (II-4) carried COL4A3 SNP M1209I. Paternity testing confirmed the parent–child relationship between the proband (II-2) and her parents (I-1, I-2). Then, the novel GLA mutation was validated de novo.

Discussion

The proband (II-2) was a 41-year-old female presenting with renal involvement and Fabry symptoms with proteinuria, hematuria, chronic pain in childhood, hypohidrosis, tinnitus, vertigo, fatigue, hypertension, left ventricular hypertrophy, typical laminated myelin inclusions in glomerular visceral epithelial cells and lower α-Gal A indicated the diagnosis of FD; while the diffuse thinning of GBM with positive staining of collagen Type IV α3 and α5 chains supported the diagnosis of TBMN. Screening of the pedigree indicated the GLA mutation 1208 ins 21 bp carried by II-2 and III-1 is a de novo pathogenic mutation.

The diagnosis of FD could be confirmed by analysis of α-Gal A activity in the vast majority of affected males; females may have (near) normal activity of the enzyme, so they should be identified through pathological examination and genetic analysis. Because of the variable and non-specific symptoms of FD females, they are usually under-diagnosed or diagnosed with a delay of up to 16.3 years [9]. In our proband, the onset of chronic pain occurred >30 years before diagnosis, while hypohidrosis, tinnitus and vertigo persisted almost 20 years before the detection of FD by renal biopsy. Our case shows that renal biopsy, especially with EM, is very important to the detection of Fabry nephropathy in the early stage and in female patients.

TBMN is the most frequent cause of microscopic hematuria in both children and adults. It has been reported to be concomitant with IgA nephropathy, minimal change glomerulopathy, focal segmental glomerulosclerosis and other
glomerular diseases [6, 7]. To the best of our knowledge, there is no report describing the occurrence of thinning of the GBM in FD. TBMN could be obscured in the early stage or in female carriers of X-linked Alport syndrome. Indirect IF studies for COL4A3 and COL4A5 and genomic DNA screening for COL4A3, COL4A4 and COL4A5 could help to differentiate them [7, 10]. Microhematuria is quite rare in Fabry patients. Our study identified that the polymorphism, COL4A3 3627G>C, was carried in four members of the family (I-1, II-2, II-4 and III-1), and three of them (II-2, II-4 and III-1) had microscopic hematuria. Diffuse thinning of the GBM was identified in renal biopsy of the proband. Therefore, the occurrence of a thin GBM in FD patients was confirmed. Our survey suggests that in FD patients with hematuria, especially familial hematuria, the status of the co-existence with a thin GBM should be identified by EM on renal biopsy.

Acknowledgements. We thank Xin Zheng and Jie E for their technical assistance in preparing renal biopsy; Lin-chang Liu for his help in the measurement of GBM thickness; Yu Huang for his help in detecting the enzyme activity; Prof Wan-zhong Zou for his comments in this manuscript. This study was supported by a project of the National Natural Science Foundation of China (#30670982).

Conflict of interest statement. None declared.

References


Table 1. Novel findings of gene analysis in the proband

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Gene</th>
<th>Location</th>
<th>Genomic nucleotide change</th>
<th>Amino acid change</th>
<th>Heterozygosity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1208ins21 bp</td>
<td>GLA</td>
<td>Ex 7</td>
<td>1208ins21 bp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1209I</td>
<td>COL4A3</td>
<td>Ex 42</td>
<td>3627G&gt;C</td>
<td>Met→Ile</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Fig. 1. Morphology of renal biopsy of the proband. (A) LM shows cytoplasmic vacuolization of glomerular visceral epithelial cells (†). PASM × 400; (B) EM shows laminated myelin inclusions in some of the podocytes (†) but not in others (asterisk). Magnification × 4000; (C) The uniform thinning of the GBM with dense inclusions in glomerular endothelial cells (†) by EM. Magnification ×12 000; (D) The laminated myelin inclusions accumulate in the cytoplasm of the podocytes (†) with the thin GBM by EM. Magnification ×12 000.

Table 1. Novel findings of gene analysis in the proband

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Gene</th>
<th>Location</th>
<th>Genomic nucleotide change</th>
<th>Amino acid change</th>
<th>Heterozygosity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1208ins21 bp</td>
<td>GLA</td>
<td>Ex 7</td>
<td>1208ins21 bp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1209I</td>
<td>COL4A3</td>
<td>Ex 42</td>
<td>3627G&gt;C</td>
<td>Met→Ile</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Fig. 2. Pedigree of the family. †: the proband; heterozygous with COL4A3 variants; heterozygous with GLA mutations; HU: hematuria; PU: proteinuria; the underlined numbers: individuals with analysis of α-Gal A and genomic DNA study.
Malignant hypertension secondary to renovascular disease during infancy— an unusual cause of failure to thrive

Elisabeth Day, Suzanne Stephens, Susan P.A. Rigden, John F. Reidy and Manish D. Sinha

Department of Paediatric Nephrology, Evelina Children’s Hospital, Guys and St Thomas’ NHS Foundation Trust, London, UK

Correspondence and offprint requests to: Manish D. Sinha; E-mail: manish.sinha@gstt.nhs.uk

Abstract

An 11-month-old girl presented with a history of failure to thrive, vomiting, polydipsia, polyuria and visual inattention. She was found to have malignant hypertension due to unilateral renal artery stenosis. This was successfully treated with percutaneous transluminal balloon angioplasty. Nearly 10 years following this initial presentation, she remains normotensive on no anti-hypertensive medications.

Keywords: failure to thrive; angioplasty; renovascular hypertension

Case report

An 11-month-old Caucasian girl presented with history of intermittent vomiting and irritability over the preceding 6 weeks. The parents reported no recent weight gain and this was confirmed on review of weight charts from parent held records. Her weight had been static over the preceding 5 months and had fallen from the 90th to 10th percentile [1]. She was the second child of non-consanguineous parents, born by normal vaginal delivery at 37 weeks gestation with birth weight of 3.05 kg (50th percentile) [1]. The week prior to admission, she had developed excessive thirst and frequent voiding.

She was pale, thin and dehydrated with visual inattention and failure to fix and follow a light source but had no dysmorphic features or stigmata of neurocutaneous disease. Cardiovascular examination was normal with no murmurs or bruits. Systolic blood pressure (BP) was 230 mmHg (95th percentile for age 106/67 mmHg) [2], urinalysis showed 3+ haematuria and 3+ proteinuria, blood investigations showed haemoglobin 15.7 g/dL (10.5–13.5), sodium 127 mmol/L (135–145), potassium 3.4 mmol/L (3.5–5.0), urea 6.6 mmol/L (1.7–8.3), creatinine 49 μmol/L (18–48) and albumin 46 g/L (40–52). Following rehydration with 0.9% saline, her systolic BP improved to 170 mmHg and blood results showed haemoglobin 10.7 g/dL, sodium 139 mmol/L, potassium 2.4 mmol/L, urea 3.4 mmol/L, creatinine 30 μmol/L and albumin 25 g/L. She was commenced on labetalol infusion and systolic BP was slowly reduced to 120 mmHg over 4 days. During this period, her anti-hypertensive therapy was converted to three oral anti-hypertensive agents to maintain adequate BP control.

Visual inattention resolved within 12 h of commencing treatment. Her fundoscopy examination was normal. Echocardiography revealed severe left ventricular hypertrophy. Renal ultrasound (US) showed right kidney 5.3 cm in length with normal sonographic appearances and large left kidney, 7.3 cm in length, with increased cortical echogenicity. It was not possible to visualize renal arteries with doppler US, 99mTc dimercaptosuccinic acid (DMSA) scan reported an irregular shaped right kidney with 45% function and normal left kidney. Digital subtraction angiography (DSA) demonstrated severe right renal artery stenosis (RAS) probably secondary to fibromuscular dysplasia (FMD) with normal left renal artery and aorta (Figure 1a). No other abnormalities involving other arterial beds were noted.

A successful right renal artery percutaneous transluminal balloon renal angioplasty (PTRA) was performed using a 3.5 mm × 9 mm coronary balloon catheter via left common