ORIGINAL ARTICLE

First report of collapsing variant of focal segmental glomerulosclerosis triggered by arbovirus: dengue and Zika virus infection

Stanley de Almeida Araújo1,2, Thiago Macedo e Cordeiro2, André Rolim Belisário2, Roberto Ferreira de Almeida Araújo1,2, Paula Eillanny Silva Marinho3, Erna Geessien Kroon3, Danilo Bretas de Oliveira4, Mauro Martins Teixeira2,5 and Ana Cristina Simões e Silva2

1Instituto de Nefro Patologia, Belo Horizonte, Brazil, 2Laboratório Interdisciplinar de Investigação Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais, Brazil, 3Departamento de Microbiologia, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, 4Faculdade de Medicina de Diamantina, Universidade Federal dos Vales do Jequitinhonha e Mucuri, Diamantina, Brazil and 5National Institute of Science and Technology in Dengue, Laboratory of Immunopharmacology, Institute of Biological Sciences, UFMG, Brazil

Correspondence and offprint requests to: Ana Cristina Simões e Silva; E-mail: acsilva@hotmail.com

ABSTRACT

Background. The collapsing variant of focal segmental glomerulosclerosis (FSGS) is the most aggressive form of FSGS and is characterized by at least one glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia. Viruses can act as aetiological agents of secondary FSGS. This study aims to establish an aetiological link between dengue virus (DENV) infection and the collapsing variant of FSGS and to analyse possible influences of the apolipoprotein 1 (APOL1) gene risk alleles on the disease.

Methods. Biopsies and medical records were gathered from 700 patients of the Instituto de Nefropatologia, Belo Horizonte, Brazil. Screening for the collapsing variant of FSGS was performed and serological, immunohistochemical, tissue polymerase chain reaction (PCR) and genetic analysis were conducted.

Results. Eight patients were identified with positive DENV serology and negative serological and/or tissue markers for hepatitis B virus, hepatitis C virus, Epstein–Barr virus, human immunodeficiency virus, cytomegalovirus and parvovirus B19. In PCR analysis, six patients had positive markers for DENV strain genetic material, one patient had positive markers for co-infection of Zika virus (ZIKV) and DENV and one patient had positive markers only for ZIKV infection. Six of the eight patients did not show risk alleles of the APOL1 gene. One patient had only one risk allele (G1) and the sample from another did not contain enough DNA for genetic analysis to be performed.

Received: 5.6.2018. Editorial decision: 12.9.2018

© The Author(s) 2018. Published by Oxford University Press on behalf of ERA-EDTA. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Conclusions. This study provided strong evidence that DENV can infect renal tissue and possibly functions as a second hit to the development of the collapsing variant of FSGS. Nonetheless, this study also highlights the possible implication of ZIKV infection in FSGS and supports the argument that risk alleles of the APOL1 gene may not be implicated in the susceptibility to FSGS in these patients.

Keywords: arbovirus, chronic kidney disease, dengue infection, focal segmental glomerulosclerosis, renal histopathology

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is defined by a morphological pattern of injury in one or more glomeruli that consists of the occlusion of glomerular capillary loops by sclerotic material [1]. FSGS is mainly associated with a healing process that directly or indirectly involves podocyte injury [1]. The collapsing variant of FSGS is the most aggressive form of the disease and is characterized by at least one glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia [2]. It is known that viruses can act as aetiological agents of secondary FSGS. Examples of viruses that cause this disease are hepatitis B (HBV) [3] and C (HCV) [4] viruses, cytomegalovirus (CMV) [5], human immunodeficiency virus (HIV) [6], Epstein–Barr virus (EBV) [7] and parvovirus B19 (PV B19) [6].

Dengue virus (DENV) and Zika virus (ZIKV) are positive-sense RNA viruses of the Flavivirus genus and Flaviviridae family that are transmitted by the Aedes aegypti mosquito vector. Infection with these viruses produces a wide spectrum of acute or subacute manifestations, ranging from an asymptomatic or self-limited non-severe clinical course to severe symptoms. In the case of dengue, the disease can be subdivided into three syndromes: dengue fever, dengue haemorrhagic fever and dengue shock syndrome [8].

Despite the abundance of acute or subacute clinical cases reporting kidney injury and acute glomerulopathies [9, 10], most of them involving interstitial and tubular damage, data are scarce on chronic pathological findings of glomerular, epithelial and podocyte damage as a consequence of dengue infection. To the best of our knowledge, no previous study has associated DENV with FSGS. Herein we present for the first time, a series of eight cases of collapsing FSGS clearly associated with renal tissue positivity to Flavivirus genus: six positive to DENV, one to ZIKV and one to both DENV and ZIKV. In addition, we investigate whether polymorphisms of the apolipoprotein 1 (APOL1) gene may have a role in collapsing FSGS triggered by DENV and ZIKV.

MATERIALS AND METHODS

Biopsy specimens were gathered from a total of 700 renal biopsies conducted in the Renal Pathology Institute during the first semester of 2016. Of these, 68 biopsies were diagnosed as FSGS and were analysed further, as described in the ‘Results’ section. All patients had been investigated for recent [immunoglobulin M (IgM) antibodies] DENV, HBV, HCV, CMV, PV B19 and HIV using commercial enzyme-linked immunosorbent assay–based techniques. Serology for ZIKV was not routinely available in 2016. In patients in whom CMV serology was not carried out, biopsies were subjected to immunohistochemistry for the detection of CMV antigens to rule out this infection. The ethics committee of the Universidade Federal de Minas Gerais approved the study, which adhered to the Declaration of Helsinki. Informed consent was obtained from all included patients.

RESULTS

In 2016, Belo Horizonte experienced the largest epidemic of dengue in its history and there was also co-circulation of ZIKV towards the end of the epidemic period [13]. Initially 68 biopsies were identified as FSGS. These patients were evaluated further for dengue positivity. Thirteen patients were found to be IgM positive for DENV and negative for all of the other viral infections tested (Figure 1). Among these 13 patients who were IgM positive for DENV with FSGS, 1 patient had the Tip variant of...
FSGS, 1 showed FSGS not otherwise specified (NOS) variant and 11 showed collapsing FSGS (Figure 2).

Eleven renal tissue specimens with the collapsing variant of FSGS were tested further to detect viruses of the Flavivirus genus by a semi-nested PCR targeting the NS5 region for differential detection of DENV types [11]. The presence of ZIKV in renal tissue was also investigated by real-time PCR [12]. Among 11 renal tissue specimens, 8 were positive for viruses of the Flavivirus genus. Of these, six were positive for only DENV, one was positive for only ZIKV and one was positive for both DENV and ZIKV (Figure 1).

Table 1 shows the molecular and serological diagnoses of the eight cases, with renal tissue positivity for viruses of the Flavivirus genus and the collapsing variant of FSGS. Renal tissue PCR analysis for DENV showed three cases of DENV-1, three cases of DENV-2 and one case of DENV-3 (Table 1). The seventh case was positive for DENV-2 and also for ZIKV (Table 1). The eighth case was positive for a Flavivirus genus virus, but was negative for DENV and positive for only ZIKV (Table 1).

As shown in Figures 2 and 3, histological findings of the collapsing variant of FSGS associated with renal tissue positivity for viruses of the Flavivirus genus were similar to those observed in other forms of this variant of FSGS. There was dilatation of Bowman’s space with glomerular collapse and podocyte hyperplasia and several glomeruli showing collapsing glomerulopathy and tubular dilatation. Immunofluorescence showed trapping of C3 in the mesangial spaces (Figure 2). There was diffuse effacement of podocytes on electron microscopy (Figure 3).

The wild-type allele for APOL1 has no correlation with renal disease, but studies suggest a strong relationship between the G1 and G2 variant alleles and the development of renal diseases [14], especially FSGS [15]. Among the studied patients, one (14%) had APOL1 risk alleles and six (86%) had no risk alleles (Table 2).

The outcome data of these eight patients were also evaluated. Seven patients evolved to advanced stages of chronic kidney disease (CKD) about 2 years after their renal biopsies. Six patients were at CKD Stage 4 (creatinine clearance < 30 mL/min)
with significant proteinuria and one patient had already been submitted for renal transplantation. Five among the six patients at CKD Stage 4 are currently being prepared for haemodialysis. Only one among the eight patients still has preserved renal function, with an average proteinuria of 500 mg/24 h. No association with any specific virus and prognosis was found. The six patients at CKD Stage 4 included two cases of DENV2 infection, one of DENV1, one of DENV3, one of ZIKV and one of co-infection with ZIKV and DENV2. The patient submitted for renal transplantation had previous infection with DENV1, whereas the case that still had preserved renal function and mild proteinuria was also infected with DENV1.

**DISCUSSION**

Our findings were gathered when Brazil was going through one of the most intense epidemics of dengue, particularly in Minas Gerais (MG) state [13]. While there was a total of 1 487,673 probable cases of Dengue in Brazil from March to October 2016, ~35% of this total (527,022 cases) took place in MG. The incidence in Belo Horizonte was extremely high, with >6% incidence in the year 2016. There was evidence of ZIKV infection towards the end of the transmission period in that year [13]. Because of the very large number of cases (>150,000 reported cases in 2016), it is reasonable that atypical or unpredictable manifestations of the disease, such as the collapsing variant of FSGS triggered by DENV, could be seen.

Although there are many possible causes of this type of FSGS, the collapsing variant is highly suggestive of viral aetiology and is most frequently associated with HIV and PVB19 infection [2]. The link between a specific form of glomerulonephritis and an occult viral aetiology can be made by the presence of viral nucleic acids in renal tissue and in peripheral blood mononuclear cells, despite the complete absence of detectable systemic viraemia by standard PCR amplification techniques [16]. Dengue infection is classically described as an acute infection, with a short period of viraemia during the febrile phase that ends by the third day after the beginning of symptoms [17]. Several clinical manifestations occur when viral levels are undetectable in peripheral blood [17]. In addition, DENV nucleic acid in peripheral blood mononuclear cells is undetectable during the convalescence period [18]. Among the eight cases presented here, three patients had no history of symptomatic dengue and four developed kidney injury symptoms 2, 4, 5 and 12 weeks following complete resolution of DENV infection symptoms. In the case of Patient 8, in which there was positivity for ZIKV and negativity for DENV in tissue PCR, no history of symptomatic viral infection was reported. These chronological findings suggest that the antigenic material

**Table 1. Molecular and serological diagnosis of viral agents**

| Patient | PCR dengue | PCR ZIKV | HBsAg | Anti-HBs | Anti-HBC | Anti-HVC | Anti-HIV-1 and -2 | CMV (lgM) | CMV tissue PCR | PVB19 |
|---------|------------|----------|-------|---------|---------|---------|-------------------|-----------|----------------|-------|
| 1       | Positive DENV-2 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 2       | Positive DENV-1 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 3       | Positive DENV-3 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 4       | Positive DENV-1 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 5       | Positive DENV-2 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 6       | Positive DENV-1 | Negative | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 7       | Positive DENV-2 | Positive | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |
| 8       | Negative | Positive | Negative | Negative | Negative | Negative | Negative | – | Negative | Negative |

**Table 2. Molecular characteristics of patients and APOL1 risk status**

| Patient | rs7385319 | rs60910145 | rs71786313 | APOL1 | APOL1 | APOL1 | APOL1 | Risk alleles |
|---------|-----------|-------------|-------------|-------|-------|-------|-------|-------------|
| 1       | AA        | TT          | 0           | TTATAA/TTATAA | 0 | 0 |
| 2       | AA        | TT          | 0           | TTATAA/TTATAA | 0 | 0 |
| 3       | AA        | TT          | 0           | TTATAA/TTATAA | 0 | 0 |
| 4       | AA        | TT          | 0           | TTATAA/TTATAA | 0 | 0 |
| 6       | AG        | TG          | 1           | TTATAA/TTATAA | 0 | 1 |
| 8       | AA        | TT          | 0           | TTATAA/TTATAA | 0 | 0 |

aNon-synonymous amino acid substitutions S342G (rs7385319) and I384M (rs60910145).
bDeletion of amino acid residues N388 and Y389 (rs71786313).
of the viruses, such as the viral RNA found in renal tissue, might be able to trigger FSGS.

In an attempt to exclude other possible viral aetiologies, we gathered medical data reporting blood and serum analyses from the time when the biopsies happened. Patients were HBV, HCV and HIV negative. Three patients were tested for CMV serology, with negative results, and all biopsy specimens were tested with immunohistochemistry for CMV, also showing negative results. PVB19 infection was investigated by renal tissue PCR analysis that indicated no presence of the virus in the specimens. We found no data regarding serology testing for EBV, but, as discussed by Chandra et al. [19], evidence linking EBV infection and the collapsing form of FSGS is very scarce.

Very few data are available regarding an effect of ZIKV on kidney cells. To date, only two studies have reported that ZIKV is able to infect tubular, podocyte, epithelial and mesangial human cells in vitro, supporting the notion that the kidney may serve as an amplification reservoir [20, 21]. These findings are in accordance with the prolonged period during which ZIKV can be detected in the urine compared with serum [22]. The positivity for ZIKV in renal tissue occurring at the same time as the detection of DENV in Patient 7 raises the question of whether ZIKV also plays a role in the collapsing variant of FSGS. However, in Patient 8, despite positive serology for DENV, only positivity for ZIKV was found in renal tissue PCR. It is well known that cross-reaction in serological tests between DENV and ZIKV is not uncommon. Therefore we believe that the possibility of ZIKV infection should be investigated further in renal tissues of patients with unexplained FSGS, mostly in epidemic scenarios.

The analysis of patient outcomes indicates a bad prognosis for the collapsing variant of FSGS associated with DENV and ZIKV infection. The prognosis seems to be similar to that of previous reports of the collapsing form of FSGS [23, 24]. Despite the small number of patients, we did not find any association between previous infection with DENV strains and ZIKV and disease outcome. When compared with HIV-associated collapsing FSGS, which is probably the best studied virally induced disease, the prognosis seems to be almost the same. Carbone et al. [24] previously reported that only 4 among 26 patients (15.4%) with HIV-induced collapsing FSGS evolved preserved renal function during follow-up, while we found only 1 of 8 patients (12.5%) in the same condition.

APOL1 is one of the six members of the APOL gene family and plays a role in the lysis of trypanosomes [14]. APOL1 is the only secreted member of the family and is produced systemically and locally in the kidney [15]. The wild-type allele for APOL1 has no correlation with kidney disease, but studies have pointed to a strong relationship between the G1 and G2 variant alleles and the development of kidney diseases [25], especially FSGS [26]. Furthermore, studies showing the collapsing variant of FSGS as being associated with HIV and PVB19 have proposed
a link between the APOL1 risk variants and infection with these viruses. The presence of risk variants of APOL1 is considered the first hit and the virus infection functions as the second hit that triggers the development of renal disease [27, 28]. Therefore we analysed a possible link between dengue infection and the genetic predisposition of our patients. There was no association between risk variants and infection, as none of our patients were homozygous for any of the risk variant alleles. However, some epidemiological and historical aspects must be taken into account. These risk variants of APOL1 are frequent among African populations [23] and, considering the genetic origins of the Brazilian population, it is intuitive to hypothesize about the presence of these alleles among these individuals. According to the colonization process of the American continent, it is possible to determine that Brazilians and Americans exhibit, as the constituent bases of their populations, three main ethnicities: Europeans, Indians and Africans. However, it is important to highlight that there are genotype and phenotype differences between the black populations of Brazil and the USA that date back to the colonization process of both regions. Genetic and historical documents indicate that more African-descent Americans’ ancestors came from different geographical locations within the African continent than African-descent Brazilians [29]. While most African Americans are descended from ancestors from the northeastern region of Africa, in Brazil, especially in the southeast region where our study took place, African-descendants’ ancestors primarily came from the African territory previously called Angola Coast, located on the central western side of Africa, as illustrated in Figure 5. This historical difference between Brazil and the USA probably interfered with the genetic pool of both countries, which in turn might have contributed to differences in FSGS. In this regard, a cross-sectional study conducted in Africa identified that APOL1 risk variants are very frequent among the population that resides in the region of ancestral origin of American African descendants. In contrast, the frequency of risk variants is very low in the ancestral region of Brazilian African descendants [30]. Indeed, previous reports in Brazil did not find an association between risk variants of APOL1 and the collapsing variant of FSGS [31]. Further studies are necessary to investigate genetic risk factors in the Brazilian population.

The mechanisms by which DENV may cause FSGS are unclear, since there are no data in the literature. HIV is currently the best studied virus with regard to renal diseases. Studies have shown the expression of viral genes in kidney cells, inducing podocyte proliferation and dedifferentiation, apoptosis and fibrosis [32]. However, HIV has a very different structure than DENV, which makes their comparison very difficult. From the viral agents that have already been linked with the development of FSGS, the most structurally similar to DENV is HCV, a Flavivirus composed of a 10-kb single positive RNA strand [33]. The mechanisms by which HCV infection produces kidney tissue damage are still unknown [33]. A possible link between viral infection and the collapsing variant of FSGS is activation of the complement cascade, resulting in deposition in renal tissue. Indeed, the presence of mesangial deposition of the C3 fraction of complement is characteristic of the collapsing variant of FSGS [17], and was also detected in our cases.

Podocyte injury is the major pathogenetic factor of FSGS [17]. Bariety et al. [34] previously showed that podocytes in collapsing glomerulopathy express macrophagic-associated markers of the CD68 cluster, suggesting that these cells are metaplastic podocytes that may have acquired the ability to process and present antigens. In this context, DENV might enter into podocytes, as all DENVs are capable of infecting host cells that express antigen-presenting cell surface proteins like dendritic cell-specific intercellular adhesion molecule (ICAM)-3-grabbing non-integrin (DC-SIGN) and mannose receptors [35]. DC-SIGN is a receptor for DENV and the expression of this receptor can be induced in podocytes during DENV infection [36, 37].

Finally, this study provided strong evidence that DENV can infect renal tissue and possibly functions as a second hit to the development of the collapsing variant of FSGS. Nonetheless, this study highlights the possible implication of ZIKV infection in one of our cases. Also, we believe that the role of APOL1 risk variants as markers of predisposition for the occurrence of FSGS may have less importance in the Brazilian population. This issue must be further investigated. The pathophysiologic mechanisms of arbovirus infections and their organ-specific complications have not yet been fully elucidated. As neglected diseases, research on these infections has received little economic and political support. However, arboviruses represent an important socio-economic problem in developing and underdeveloped countries, and many of their consequences are still unknown. DENV infection should be considered in cases of the collapsing variant of FSGS that occur in countries with a high prevalence of dengue.

FUNDING

This study was partially supported by grants from the Brazilian National Research Council, Fundação de Amparo à Pesquisa do Estado de Minas Gerais and the National Institute of Science and Technology in Dengue. M.M.T. and A.C.S.e.S. are recipients of productivity research fellowships from the Brazilian National Research Council. The results presented in this article have not been published previously in whole or part, except in abstract form.

AUTHORS’ CONTRIBUTIONS

S.d.A.A and A.C.S.e.S were responsible for the research idea and study design. T.M.e.C and R.F.d.A.A were responsible for data acquisition. S.d.A.A was responsible for histological analysis. P.E.S.M and D.B.d.O were responsible for extraction of genetic material. A.R.B was responsible for genetic analysis. T.M.e.C., A.R.B., R.F.d.A.A. and D.B.d.O. were responsible for data analysis and interpretation. E.G.K., M.M.T. and A.C.S.e.S. were responsible for supervision or mentorship.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Angioi A, Paní A. FSGS: from pathogenesis to the histological lesion. J Nephrol 2016; 29: 517–523
2. D’Agati VD, Fogo AB, Bruijn JA et al. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis 2004; 43: 368–382
3. Khaira A, Upadhyay BK, Sharma A et al. Hepatitis B virus associated focal and segmental glomerular sclerosis: report of two cases and review of literature. Clin Exp Nephrol 2009; 13: 373–377

Downloaded from https://academic.oup.com/ckj/advance-article-abstract/doi/10.1093/ckj/sfy104/5193070 by guest on 05 May 2019
4. Sperati CJ. Stabilization of hepatitis C associated collapsing focal segmental glomerulosclerosis with interferon alpha-2a and ribavirin. Clin Nephrol 2013; 80: 231–234
5. Dettrmar AK, Oh J. Infection-related focal segmental glomerulosclerosis in children. Biomed Res Int 2016; 2016: 7351964
6. Wyatt CM, Meliambro K, Klotman PE. Recent progress in HIV-associated nephropathy. Annu Rev Med 2012; 63: 147–159
7. Joshi A, Arora A, Cimbalka D et al. Acute Epstein-Barr virus infection-associated collapsing glomerulopathy. Clin Kidney J 2012; 5: 320–322
8. World Health Association. Dengue: guidelines for diagnosis, treatment, prevention and control. 2009. http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf (3 May 2018, date last accessed)
9. Futrakul P, Poshyachinda V, Mitrakul C et al. Renal involvement and reticulo-endothelial-system clearance in dengue hemorrhagic fever. J Med Assoc Thai 1973; 56: 33–39
10. Boonpucknavig V, Bhamarapravati N, Boonpucknavig S et al. Origin and dynamics of admixture in Brazilians and its effect on the pattern of deleterious mutations. Proc Natl Acad Sci USA 2015; 112: 8698–8701
11. Bronzoni RVdM, Baleotti FG, Ribeiro Nogueira RM et al. Duplex reverse transcription-PCR followed by nested PCR assays for detection and identification of Brazilian alphaviruses and flaviviruses. J Clin Microbiol 2005; 43: 696–702
12. Lanciotti RS, Kosoy OL, Laven JJ et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia. Emerg Infect Dis 2007; 14: 1232–1239
13. Prevenção e combate Dengue, Chikungunya e Zika. Boletim Epidemiológico 2016; 47: 38. http://combateaedes.saude.gov.br/images/pdf/2016-Dengue_Zika_Chikungunya-SE49.pdf (3 May 2018, date last accessed)
14. Duchateau PN, Pullinger CR, Cho MH et al. Apolipoprotein L gene family: tissue-specific expression, splicing, promoter regions; discovery of a new gene. J Lipid Res 2001; 42: 620–630
15. Limou S, Dummer P, Nelson GW et al. APOL1 toxin, innate immunity and kidney injury. Kidney Int 2015; 88: 28–34
16. Fowell AJ, Sheron N, Rosenberg WM. Renal hepatitis C in the absence of detectable serum or hepatic virus. Liver Int 2008; 28: 889–891
17. Lum LCS, Ng CJ, Khoo EM. Managing dengue fever in primary care: a practical approach. Malays Fam Physician 2014; 9: 2–10
18. Perdomo-Celis F, Salgado DM, Narváez CF. Magnitude of viremia, antigenemia and infection of circulating monocytes in children with mild and severe dengue. Acta Trop 2017; 167: 1–8
19. Chandra P, Kopp JB. Viruses and collapsing glomerulopathy: a brief critical review. Clin Kidney J 2012; 6: 1–5
20. Chen J, Yang Y-F, Chen J et al. Zika virus infects renal proximal tubular epithelial cells with prolonged persistency and cytopathic effects. Emerg Microbes Infect 2017; 6: e77
21. Alcendor DJ. Zika virus infection of the human glomerular cells: implications for viral reservoirs and renal pathogenesis. J Infect Dis 2017; 216: 162–171
22. Zhang FC, Li XF, Deng YQ et al. Excretion of infectious Zika virus in urine. Lancet Infect Dis 2016; 16: 641–642
23. Thomas DB, Franceschini N, Hogan SL et al. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int 2006; 69: 920–926
24. Carbone L, D’agati V, Cheng J-T et al. Course and prognosis of human immunodeficiency virus-associated nephropathy. Am J Med 1989; 87: 389–395
25. Genovese G, Friedman DJ, Ross MD et al. Association of trypanolytic Apol1 variants with kidney disease in African-Americans. Science 2010; 329: 841–845
26. Kopp JB, Winkler CA, Zhao X. Clinical features and histology of apolipoprotein L1-associated nephropathy in the FS9S clinical trial. J Am Soc Nephrol 2015; 26: 1443–1448
27. Besse W, Mansour S, Jatwani K et al. Collapsing glomerulopathy in a young woman with APOL1 risk alleles following acute parovirus B19 infection: a case report investigation. BMC Nephrol 2016; 17: 125
28. Fine DM, Wasser WG, Estrella MM et al. APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. J Am Soc Nephrol 2012; 23: 343–350
29. Kehdy FSG, Gouveia MH, Machado M et al. Origin and dynamics of admixture in Brazilians and its effect on the pattern of deleterious mutations. Proc Natl Acad Sci USA 2015; 112: 8698–8701
30. Kruzel-Davila E, Wasser WG, Skorecki K. APOL1 nephropathy: a population genetics and evolutionary medicine detective story. Semin Nephrol 2017; 37: 490–507
31. Colares VS, Titan SMD, Pereira AD et al. MHY9 and APOL1 gene polymorphisms and the risk of CKD in patients with lupus nephritis from an admixture population. PLoS One 2014; 9: e87716
32. Mikulak J, Singhal PC. HIV-1 and kidney cells: better understanding of viral interaction. Nephron Exp Nephrol 2010; 115: e15–e21
33. Barsoum RS. Hepatitis C virus: from entry to renal injury—facts and potentials. Nephrol Dial Transplant 2007; 22: 1840–1848
34. Bariety J, Nochy D, Mandet C et al. Podocytes undergo phenotypic changes and express macrophage-associated markers in idiopathic collapsing glomerulopathy. Kidney Int 1998; 53: 918–925
35. Cruz-Oliveira C, Freire JM, Conceição TM et al. Receptors and routes of dengue virus entry into the host cells. FEMS Microbiol Rev 2015; 39: 155–170
36. Cheung KT, Sze DM, Chan KH et al. Involvement of caspase-4 in IL-1 beta production and pyroptosis in human macrophages during dengue virus infection. Immunobiology 2017; 223: 356–364