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SARS-CoV-2 and Fabry nephropathy: potential risks and the pathophysiological perspective

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ABSTRACT

Fabry disease is an X-linked disorder due to mutations in alpha-galactosidase A gene. It affects the kidney in virtually all patients with classical and some late onset variants. Podocytes, endothelial cells, vascular smooth muscle, tubular and mesangial cells are involved in different ways. Proteinuria and chronic kidney disease are the result of the progressive accumulation of the enzyme substrates globotriaosylceramide (GB3) and lyso-GB3 in the cytoplasm of these cells (mainly in lysosomes), which leads to cellular and organ dysfunction and eventually renal failure and end-stage kidney disease. Specific enzyme replacement therapy and pharmacological chaperone are at present the main therapeutic approach. After enzyme infusion, the delivered enzyme is differentially uptaken by kidney cells in three different ways: By Mannose-6-phosphate receptor, megalin and sortilin. The delivered enzyme gradually clears cells from the accumulation of the glycosphingolipids and contributes to a cellular healthier status. The recent pandemic caused by SARS-CoV-2 has led to the collapse of health systems around the world and to thousands of deaths. Kidney involvement has been reported to range from proteinuria to acute kidney injury, 30% of which may require renal replacement therapy. In this review the potential causes for which Fabry patients should be at increased risk and the necessity not to discontinue therapy are discussed.

Implication for health policy/practice/research/medical education:
Fabry patients may be at increased risk of kidney morbidity during SARS-CoV-2 infection. Proteinuria and blood pressure may increase, and sodium and bicarbonate balance may be threatened, particularly at advanced stages of chronic kidney disease.

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Review

Coronavirus

Three coronaviruses have crossed species causing pneumonia in humans in the last 20 years: severe acute respiratory syndrome coronavirus (SARS-CoV) (1), Middle-East respiratory syndrome coronavirus (2,3) (MERS-CoV), and recently SARS-CoV-2 (4). The rapid spread of these infections may be due to globalization and to daily fast air travelling. SARS-CoV emerged in China in 2002, MERS-CoV appeared in Arabia in 2012, and SARS-CoV-2 in late 2019 in China, may be transmitted from bats to humans (5). SARS-CoV-2 is associated with an ongoing outbreak of atypical pneumonia (COVID-2019) that has affected over 3 4000 000 people and killed more than 242 000 in >150 countries as of May 3, 2020.

SARS-CoV-2 strategies to enter human cells

Coronavirus entrance to host cells is mediated by the transmembrane spike (S) glycoprotein that forms homotrimers protruding from the viral surface (6). S comprises two functional subunits responsible for binding to the host cell receptor (S1 subunit) and fusion of the viral and cellular membranes (S2 subunit) (7). Further cleavage at the S2 subunit has been proposed to activate the protein for membrane fusion via extensive irreversible changes that pertain to the endocytosis processes (7). As a result, coronavirus entry into susceptible cells requires the participation of receptor-binding and proteolytic processing of the S protein to promote virus-cell fusion. Binding affinity between SARS-CoV S and human

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angiotensin-converting enzyme-2 (ACE-2) was proposed to correlate with viral pathogenicity in humans (8). In addition, the virulence of SARS-CoV-2, besides coupling to receptor ACE-2, depends on the action of a serine protease TMPRSS2, which is employed by SARS-CoV-2 for S protein priming, essential for viral entry into cells and for viral spread in the host (9,10).

Besides membrane fusion, the clathrin dependent and -independent endocytosis also mediate SARS-CoV entrance to cells. Shu et al have recently been reported that SARS-CoV-2 was shown to also invade target cells by CD147, a ubiquitously expressed transmembrane glycoprotein with interaction with diverse partners such as cyclophilins, caveolin-1, and integrins (11,12).

Immune responses to SARS-CoV-2

As a result, antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells (13). Noteworthy, the number of circulating CD4+ and CD8+ T cells is reduced in an excessive activation. As disease progresses to acute respiratory distress syndrome the classical cytokine storm ensues with the release of an uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines as IFN-alpha, IFN-gamma, IL-1, IL-6, IL-12, IL-18, IL-33, TNF-alpha, TGF-beta and chemokines (14,15).

Multiple studies have documented a role for the alternate (AP) and lectin pathways (LPs) of complement in microvascular injury (16,17). Interestingly, the involvement of the LP in COVID-19 comes from the discovery that MBL (mannose binding lectin) binds to the S glycoprotein (17). A complex of MBL with MASP2 (mannose associated serine protease 2) is the first step in LP activation, and part of a positive feedback loop leading to sustained AP activation, with inflammation and concurrent activation of the coagulation cascade (17). The glycosylation sites for high-mannose structures with the potential to similarly engage MBL, and thus activate MASP2, have been identified for SARS-CoV-2 (17). Angiotensin I and angiotensin II have been associated with inflammation, oxidative stress, and fibrosis, and ACE-2 is involved in their deactivation (17). With an overwhelming clinical infection, the binding to ACE-2 on systemic epithelial targets will interfere with ACE-2 activity. The result will be an increase in angiotensin II, that in the kidney will lead to reactive oxygen species formation, inflammation and vasoconstriction signals and further complement activation (17). The potential loss of auto-vasoconstriction and regulation of kidney blood flow, coupled to complement activation through injured vascular segments would finally lead to acute renal dysfunction, hypoxemia and micro-thrombosis.

The kidney open doors to receive SARS-CoV-2

It has been shown the SARS-CoV-2 enters cells by coupling with ACE-2. The kidney is one of the most important organs in which ACE-2 is synthesized. Podocytes, proximal tubular cells and the endothelium all contain the enzyme ACE-2 (18). The physiological role of the enzyme is dual. It converts the nonapeptide angiotensin II to angiotensin 1-7, a vasodilator, and it degrades angiotensin II. This action is mainly undertaken by the endothelial and vascular smooth muscle cells. In the brush border of proximal tubular cells, it is involved in sodium balance and natriuresis. It is also located in podocytes, where its function is mainly involved in preventing the loss of proteins. Angiotensin 1-7 upregulates nephrin in the slit diaphragm, being critical for the glomerular filtration barrier physiological integrity (19). In addition, podocytes also participate as antigen-scavenger cells, and contain receptors for complement components and Fc portion of immunoglobulins. However, as the podocyte is stressed, it switches its phenotype to an antigen-presenting cell (20).

Fabry patients and SARS-CoV-2

Kidney injury has appeared relatively less with COVID-19 than with the Middle East respiratory syndrome or hantavirus infections, perhaps due to the different underlying mechanisms and ensuing pathologic manifestations. Clinically, the incidence of acute kidney injury in COVID-19 varied from 0.9% to 29% in different centres. New onset proteinuria was also reported by several institutions (21) Currently, the pathologic investigation has primarily focused on respiratory, hematopoietic, and immune systems, whereas morphologic data of kidney injury are lacking (21).

As mentioned previously, Fabry nephropathy alters all cellular compartments and renders Fabry patients at a higher risk for SARS-Co-V-2 beyond chronic kidney disease. In podocytes, ACE-2 not only counteracts angiotensin II inflammatory and hypertrophic actions, but it also upregulates nephrin. Angiotensin 1-7, induces nephrin synthesis (19). The uptake of SARS-CoV-2 by podocytes causes a functional decrease of the enzyme, freeing angiotensin II actions locally. This decrease in ACE-2 may also contribute to the increase in proteinuria, as nephrin levels are diminished by the ACE-2 decrease caused by SARS-CO-V2. In this respect, it has been reported that Fabry patients present a decrease in nephrin concentration that is in relationship with the degree of enzyme replacement therapy (22). The capacity of SARS-Co-V2 to affect podocytes is also related to autophagy, which is also dysregulated and increased in Fabry podocytes (23). This is a critical homeostatic cellular mechanism for cell survival.

The delivery and uptake of enzyme replacement therapy by podocytes is undertaken by three different mechanisms: Mannose-6-phosphate, megalin and sortilin (24). Due to the fact that SARS-CoV-2 is capable of stimulating the LP by MBL, it is assumed that the viral molecular concentration of mannose is elevated, thus competing with the uptake of the enzyme and potentially blocking its cellular entrance. In addition, the endocytic pathway is involved as another strategy of SARS-CoV-2 to invade cells (25). Clathrin participates in this process. Interestingly, podocyte megalin, a transmembrane protein that functions as a receptor for the enzyme cellular uptake, also employs clathrin for intracellular trafficking (26). Therefore, this is another potential competition between SARS-CoV-2 and enzyme replacement therapy. The proximal tubule also contains both ACE-2 and megalin, In this regard, the glomerular-tubular balance in which angiotensin II is involved will be compromised, as well as sodium and bicarbonate balance and the delivered enzyme absorption. Finally, the endothelial cell is another target both for SARS-CoV-2 and for the accumulation of alpha-galactosidase A substrates. In addition to the effects that SARS-CoV-2 causes to the podocyte and proximal tubules, the already diseased endothelial cells of Fabry patients that bear the burden of enzyme substrate effects, are at risk of further damage. It has been shown that in many primary and secondary glomerular diseases, there is a down-regulation of ACE-2 in podocytes and endothelial cells, with a resultant increase in angiotensin II levels. Moreover, the activation of complement may render these patients at a higher risk to develop thrombotic microangiopathy. The generation of knock-out mice lacking alpha-Gal A activity has provided a useful model for the study of the vasculopathy in Fabry disease (27). Although these mice do not display a spontaneous vasculopathy, they exhibit a robust thrombotic response to oxidant-induced injury (28), potentiating the oxidative stress caused by SARS-CoV-2 (17).

As mentioned previously, SARS-CoV-2 employs caveolin-1 to enter target cells, forms part of caveolae content. Caveolae are extra-lysosomal cytoplasmic locations where enzyme replacement therapy is capable of GB3 clearance (12). Finally, in Fabry nephropathy there is a local baseline increase in the concentration of the cytokines compared to the general population that SARS-CoV-2 infection additionally causes, which augments in turn the local kidney inflammation (29).

Fabry patients on chronic dialysis may present the same risks as non-dialysis ones, but probably at a higher level due to the dialysis inherent complications. Whether an increase dose of the prescribed enzyme replacement therapy is necessary during SARS-CoV-2 infection is to be determined.

Conclusion

Fabry patients may be at increased risk of kidney morbidity during SARS-CoV-2 infection. Proteinuria and blood pressure may increase, and sodium and bicarbonate balance may be threatened, particularly at advanced stages of chronic kidney disease. Enzyme replacement therapy may be compromised due to cellular uptake competition with shared viral mechanisms of cellular entrance.

Author's contribution

HT is the single author of the manuscript.

Conflicts of interest

The author declares that he has no competing interests.

Ethical consideration

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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References

1. Drosten C, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348:1967-76. doi: 10.1056/NEJMoa030747.
2. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. 3003;348:1953-66. doi: 10.1056/NEJMoa030781.
3. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-20. doi: 10.1056/NEJMoa1211721.
4. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382,:727-33. doi: 10.1056/NEJMoa2001017.
5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273. doi: 10.1038/s41586-020-2012-7.
6. Tortorici MA, Walls AC, Lang Y, Wang C, Li Z, Koerhuis D, et al. Structural basis for human coronavirus attachment to sialic acid receptors. Nat Struct Mol Biol. 2019;26:481-9. doi: 10.1038/s41594-019-0233-y.
7. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A. 2009; 106:5871-6. doi: 10.1073_pnas.0809524106.
8. Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J 2005;24:1634-43.

doi: 10.1038/sj.emboj.7600640.
9. Pan X, Xu D, Zhang H, Zhou W, Wang L, Cui X. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020 Mar 31. doi: 10.1007/s00134-020-06026-1.
10. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271-80. doi: 10.1016/j.cell.2020.02.052.
11. Wang K, Chen W, Zhou YS, Lian JQ, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv. doi: 10.1101/2020.03.14.988345. Accessed May 3, 2020.
12. Shu L, Shayman JA. Caveolin-associated accumulation of globotriaosylceramide in the vascular endothelium of alpha-galactosidase A null mice. J Biol Chem 2007;282:20960-7. doi: 10.1074/jbc.M702436200.
13. Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-associated coronavirus, N Engl J Med. 2003;349:508-9. doi: 10.1056/NEJM200307313490520.
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
15. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10:102e108. doi: 10.1016/j.jpha.2020.03.001.
16. Prüfer F, Scheiring J, Sautter S, Jensen DB, Treichl R, Würzner R, et al. Terminal complement complex (C5b-9) in children with recurrent hemolytic uremic syndrome. Sem Thromb Hemost. 2006;32:121-7. doi: 10.1055/s-2006-939768.
17. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020. doi: 10.1016/j.trsl.2020.04.007
18. Ferrario CM, Varagic J. The ANG-(1–7)/ACE2/mas axis in the regulation of nephron function. Am J Physiol Renal Physiol. 2010;298:F1297-305. doi: 10.1152/ajprenal.00110.2010
19. Giani JF, Muñoz MC, Pons RA, Cao G, Toblli JE, Turyn D, et al. Angiotensin-(1–7) reduces proteinuria and diminishes structural damage in renal tissue of stroke-prone spontaneously hypertensive rats. Am J Physiol Renal Physiol. 2011;300: F272-82. doi: 10.1152/ajprenal.00278.2010.
20. Trimarchi H. Abatacept in glomerular diseases. The open road for the second signal as a new target is settled down. Recent Pat Endocr Metab Immune Drug Discov. 2015;9:2-14. doi: 10.2174/1872214809666150302104542
21. Su H, Yang M, Wan C, Yi L, Tang F, Zhu JY, et al. Renal histopathological analysis of 26 post-mortem findings of patients with COVID-19 in China. Kidney Int. 2020; doi: 10.1016/j.kint.2020.04.003.
22. Ito S, Ogura M, Kamei K, Matsuoka K, Warnock DG. Significant improvement in Fabry disease podocytopathy after 3 years of treatment with agalsidase beta Pediatr Nephrol 2016;31:1369-73. doi: 10.1007/s00467-016-3387-4.
23. Liebau MC, Braun F, Höpker K, Weitbrecht C, Bartels V, Müller RU, et al. Dysregulated autophagy contributes to podocyte damage in Fabry's disease. PloS One 2013;8(5):e63506. doi:10.1371/journal.pone.0063506.
24. Prabhakaran T, Nielsen R, Larsen JV, Sørensen SS, Feldt-Rasmussen U, Saleem MA, et al. Receptor-mediated endocytosis of alpha-galactosidase A in human podocytes in Fabry disease. Plos One;2011;6(9):e25065. doi: 10.1371/journal.pone.0025065.
25. Yang N, Shen MH. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci. 2020. doi:10.7150/ijbs.45498.
26. Czekay RP, Orlando RA, Woodward L, Lundstrom M, Farquhar MG. Endocytic trafficking of megalin/RAP complexes: Dissociation of the complexes in late endosomes. Mol Biol Cell. 1997;8(3):517-32. doi: 10.1091/mbc.8.3.517.
27. Ohshima T, Murray GJ, Swaim WD, Longenecker G, Quirk JM, Cardarelli CO, et al. alpha-Galactosidase A deficient mice: a model of Fabry disease. Proc Natl Acad Sci USA 1997; 94:2540-4. doi: 10.1073/pnas.94.6.2540.
28. Eitzman DT, Bodary PF, Shen Y, Khairallah CG, Wild SR, Abe A, et al. Fabry disease in mice is associated with age-dependent susceptibility to vascular thrombosis. J Am Soc Nephrol. 2003;14:298-302. doi: 10.1097/01.ASN.0000043901.45141.D4.
29. Trimarchi H, Karl A, Raña MS, Forrester M, Pomeranz V, Lombi F, et al. Initially non-diagnosed Fabry's disease when electronic microscopy is lacking: the continuing story of focal and segmental glomerulosclerosis. Case Rep Nephrol Urol. 2013;3:51-57. doi:10.1159/000351516.