10.5152/turkjnephrol.2021.21113

Case Report

Turkish Journal of Nephrology

The Mutation Identified in TWEAK-Fn14 Pathway May Affect the Clinical Course of IgA Nephropathy/Henoch-Schönlein Purpura Nephritis: A Case Report

Zeynep Kendi Çelebi[1], Didem Turgut[1], Şiyar Erdoğmuş[1], Ezgi Avşaroğlu[2], Hacı Uğur Muşabak[3], Turan Çolak[1]

[1]Department of Nephrology, Başkent University School of Medicine, Ankara, Turkey
[2]Başkent University School of Medicine, Ankara, Turkey
[3]Department of Allergy and Immunology, Başkent University School of Medicine, Ankara, Turkey

ABSTRACT

The TNF-like weak inducer of apoptosis (TWEAK) gene was first discovered in 1997 and its receptor Fn14 in 2001. TWEAK can be protective or damaging, depending on the status of the tissue. While basal TWEAK and Fn14 concentrations were found to be low in the kidney under normal conditions, TWEAK levels and tissue receptor expression were found to be increased in the presence of an acute injury.We report here the first case with persistent microscopic hematuria since infancy with TWEAK gene mutation, who was diagnosed with IgA Nephropathy/Henoch-Schönlein Purpura Nephritis at the age of 18 during a kidney biopsy. The genetic mutation in this patient may have caused a better course of the disease.

Keywords: Chromosome 17, henoch schönlein nephritis, iga nephropathy, tnf-like weak inducer of apopitosis

Corresponding author: Zeynep Kendi Çelebi ✉ zeynepkendi@yahoo.com

Received: December 23, 2021 **Accepted:** June 7, 2021

Cite this article as: Kendi Çelebi Z, Turgut D, Erdoğmuş Ş, Avşaroğlu E, Muşabak HU, Çolak T. The mutation identified in tweak-Fn14 pathway may affect the clinical course of IgA nephropathy/Henoch-Schönlein purpura nephritis: A case report. *Turk J Nephrol.* 2021; 30(3): 250-252.

INTRODUCTION

IgA nephropathy (IgAN) is the most common type of glomerulonephritis in the world and also the third most common form of glomerulonephritis in Turkey.[1,2] IgAN is defined as mesangial proliferation with prominent IgA deposition, and Henoch Schonlein purpura nephritis (HSPN) is a form of IgAN. Both HSPN and IgAN show similar pathologic features and abnormal IgA glycosylation, hence differential diagnosis can be made only with clinical findings.

TNF-like weak inducer of apoptosis (TWEAK) is a type 2 transmembrane glycoprotein, a TNF superfamily member, which regulates cell proliferation, differentiation, inflammation, and apoptosis through its receptor fibroblast growth factor-inducible (Fn14).

Herein, we report a 23-year-old woman with IgAN and heterozygote TNFSF12: c.295C>T (p.R99W) gene mutation, which encodes TWEAK/APRIL protein.

CASE REPORT

When the patient was 1.5-years-old, incidentally, microscopic hematuria was detected during the examination for abdominal pain. At the follow-up period, at the age of 2, right tonsillectomy was performed, and thereafter at age of 7, left tonsillectomy was performed because of continuous microscopic hematuria and frequent throat infection.

At the age of 18, a kidney biopsy was performed due to rash beginning on the dorsal side of the legs and nephritic syndrome (macroscopic hematuria and 1 g/d proteinuria with normal GFR (glomerular filtration rate)). Pathologic examination showed mesangioproliferative glomerulonephritis class II, with IgA and C3 positivity in immunohistochemistry.

Treatment with oral corticosteroid and azathioprine resulted in complete remission. After remission, the patient suffered from ankle and lumbar pain. Magnetic

resonance examination showed unilateral sacroiliitis. The patient had HLA B51 gene positivity. Erythrocyte sedimentation rate and C-reactive protein levels were between normal limits during follow-up. The patient's IgA level was 2.67 g/L (0.65-4.21 g/L), but total IgE level was > 2000 IU/mL (normal range < 87 IU/mL). Genotyping for autoinflammatory diseases according to clinical findings was made and in 17. chromosome heterozygote TNFSF12: c.295C>T (p.R99W) gene mutation was detected. This change in the TWEAK gene is likely to cause a significant decrease in function or increase in the protein produced by this gene.

DISCUSSION

TWEAK is a cytokine that participates in proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation. The human TWEAK gene is located at chromosome 17 position p13.1 and encodes a 249-amino acid type II transmembrane glycoprotein of 30 kDa. TWEAK is synthesized intracellularly by furin protease as a transmembranous protein and thereafter quickly turned into soluble TWEAK, which mediates the physiological effects of this protein through binding to its receptor Fn14. TWEAK:Fn14 binding promotes activation of canonical and non-canonical nuclear factor-κB (NF-κB) pathways and kinase systems including mitogen-activated protein kinases, Janus kinase, JAK/signal transducer and activator of transcription, and phosphoinositide 3-kinase/Akt, thus modulating cell proliferation, death, migration, differentiation, and inflammation.[3] In kidneys, TWEAK causes proliferation and inflammation in proximal tubule cells, podocytes, and mesangial cells and also causes cell death in the proximal tubule and mesangial cells in the presence of TNFα/IFN-γ.[4]

Importantly, the specific pathways activated by the TWEAK/Fn14 axis are cell type-, cell state-, and microenvironment-dependent.[5] Both TWEAK and Fn14 are constitutively expressed at low levels in normal kidneys, and Fn14 expression is induced after kidney injury.[6] Experimental kidney disease models show different responses to the TWEAK protein, and this is thought to be influenced by the environmental factors that the cell is in during the injury period. When the interaction of TWEAK protein and Fn14 receptor was blocked using blocking antibodies or receptor knock-out mice, the acute renal injury model showed decreased inflammation and improved renal function, uninephrectomized mice showed decreased proliferation capacity of the remaining kidney, and the lupus disease model showed decreased proteinuria, inflammation, and IgG accumulation.[7-10]

The limitation of our case report is the absence of soluble and urinary TWEAK levels. Therefore, we could not clearly show the relationship between the genetic mutation and soluble TWEAK levels. In human studies, urinary TWEAK levels were higher than controls in IgAN, and suggested that high urinary TWEAK levels affect crescent formation and proteinuria in patients with IgAN.[11,12] Inflammation of IgA nephropathy has been shown to be regressed when the TWEAK pathway is inhibited by microRNA.[13] Since we do not know the level of soluble TWEAK in the blood or urine, we cannot explain the effect of the mutation we detected, on the course of the disease, but the low level of inflammation and a good prognosis for IgAN suggest that the TWEAK gene mutation in the patient results in inhibition of the gene product.

Although preclinical studies have shown promising results, the ATLAS study (ClinicalTrials.gov Identifier: NCT01499355) with humanized monoclonal TWEAK antibodies in lupus nephritis was terminated early, as it did not demonstrate sufficient efficacy to warrant continuation of the study.[14] Inhibition or activation of cytokines in these pathways may not show the expected effect.

TWEAK protein induces the secretion of inflammatory mediators in mesangial and tubular epithelial cells through activation of the Fn14 receptor. The role of TWEAK in proliferative lupus nephritis and tubular acute kidney injury has been also established.[8-10] An experimental study showed that glomerular Fn14 expression is increased in human and experimental non-immune podocyte injury and proteinuric kidney disease, and that Fn14 contributes to podocyte injury and glomerular and periglomerular inflammation. TWEAK protein appears to be related to the development of kidney damage at both the glomerular and tubular levels.[15]

In summary, our case shows a benign course with IgAN and heterozygote TNFSF12: c.295C>T (p.R99W) gene mutation. This mutation may have a protective role against inflammation. More clinical and experimental studies are needed for further diagnostic and therapeutic approaches.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept - Z.K.Ç., D.T., Ş.E., E.A., H.U.M., T.Ç.; Design - Z.K.Ç., D.T., Ş.E., E.A., H.U.M., T.Ç.; Supervision - Z.K.Ç., H.U.M., T.Ç.; Materials - Z.K.Ç., D.T., Ş.E., E.A., H.U.M., T.Ç.; Data Collection and / or Processing - Z.K.Ç., D.T., Ş.E., E.A., H.U.M., T.Ç.; Analysis and Interpretation - Z.K.Ç., D.T., Ş.E., E.A., H.U.M., T.Ç.; Literature Search - Z.K.Ç., D.T., Ş.E.; Writing - Z.K.Ç.; Critical Review - D.T., Ş.E., E.A., H.U.M., T.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. McGrogan A, Franssen CFM, De Vries CS. The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. *Nephrol Dial Transplant*. 2011;26(2):414-430. [CrossRef]

2. Ozturk S, Sumnu A, Seyahi N, et al. Demographic and clinical characteristics of primary glomerular diseases in Turkey. *Int Urol Nephrol*. 2014;46(12):2347-2355. [CrossRef]
3. Burkly LC, Michaelson JS, Zheng TS. TWEAK/Fn14 pathway: an immunological switch for shaping tissue responses. *Immunol Rev*. 2011;244(1):99-114. [CrossRef]
4. Gao HX, Campbell SR, Burkly LC, et al. TNF-like weak inducer of apoptosis (TWEAK) induces inflammatory and proliferative effects in human kidney cells. *Cytokine*. 2009;46(1):24-35. [CrossRef]
5. Burkly LC, Michaelson JS, Hahm K, Jakubowski A, Zheng TS. TWEAKing tissue remodeling by a multifunctional cytokine: role of TWEAK/Fn14 pathway in health and disease. *Cytokine*. 2007;40(1):1-16. (available at: https://linkinghub.elsevier.com/retrieve/pii/S1043466607004164). [CrossRef]
6. Justo P, Sanz AB, Sanchez-Niño MD, et al. Cytokine cooperation in renal tubular cell injury: the role of TWEAK. *Kidney Int*. 2006;70(10):1750-1758. [CrossRef]
7. Hotta K, Sho M, Yamato I, et al. Direct targeting of fibroblast growth factor-inducible 14 protein protects against renal ischemia reperfusion injury. *Kidney Int*. 2011;79(2):179-188. [CrossRef]
8. Sanz AB, Sanchez-Niño MD, Izquierdo MC, et al. Tweak induces proliferation in renal tubular epithelium: A role in uninephrectomy induced renal hyperplasia. *J Cell Mol Med*. 2009;13(9B)(9 B):3329-3342. [CrossRef]
9. Molano A, Lakhani P, Aran A, et al. TWEAK stimulation of kidney resident cells in the pathogenesis of graft versus host induced lupus nephritis. *Immunol Lett*. 2009;125(2):119-128. [CrossRef]
10. Zhao Z, Burkly LC, Campbell S, et al. TWEAK/Fn14 Interactions Are Instrumental in the pathogenesis of Nephritis in the Chronic graft-versus-host Model of systemic lupus erythematosus. *J Immunol*. 2007;179(11):7949-7958. [CrossRef]
11. Kim JS, Jeong KH. Clinical significance of urinary tumor necrosis factor-like weak inducer of apoptosis (TWEAK) in immunoglobulin A nephropathy. *Clin Nephrol*. 2020;93(2):99-105. [CrossRef]
12. Sasaki Y, Shimizu Y, Suzuki Y, Horikoshi S, Tomino Y. TWEAK/Fn14 system and crescent formation in IgA nephropathy. *BMC Nephrol*. 2015;16(1):27. [CrossRef]
13. Guo Y, Liao Y. miR-200bc/429 cluster alleviates inflammation in IgA nephropathy by targeting TWEAK/Fn14. *Int Immunopharmacol*. 2017;52(July):150-155. [CrossRef]
14. Furie R, Malvar A, Navarra SV, et al. Evaluation of the efficacy, safety, and tolerability of BIIB023 as an adjunct to standard of care in subjects with lupus nephritis. *Arthritis Rheumatol*. 2016;68(suppl 10). (available at: https://acrabstracts.org/abstract/evaluation-of-the-efficacy-safety-and-tolerability-of-biib023-as-an-adjunct-to-standard-of-care-in-subjects-with-lupus-nephritis/)
15. Sanchez-Niño MD, Poveda J, Sanz AB, et al. Fn14 in podocytes and proteinuric kidney disease. *Biochim Biophys Acta*. 2013;1832(12):2232-2243. [CrossRef]