Bölüm **8**

Otozomal Dominant Polikistik Böbrek Hastalığı: Patogenez, Klinik, Yeni Tedavi Seçenekleri

Mehmet Tuncay

• GİRİŞ

Polikistik böbrek hastalığı (PKBH), böbreğin tümünde, içi sıvı dolu kistlerin patolojik gelişimiyle karakterize, kalıtsal, monogenik bir böbek hastalığıdır. Bu kistler zamanla böbreğin büyümesine ve sonunda renal replasman tedavisi gerektiren son dönem böbrek yetmezliğine neden olmaktadır. Otozomal dominant polikistik böbrek hastalığı (ODPKBH) en sık görülen kalıtsal böbrek hastalığı olmanın yanı sıra dünyada kronik böbrek yetmezliğine neden olan hastalıklar içinde dördüncü sırada yer almaktadır. Otozomal resesif PKBH ise genel olarak antenatal veya neonatal dönemde ultrasonografi ile büyümüş ekojenik böbreklerin tespit edilmesiyle tanı konulan nadir bir hastalıktır.

ODPKBH bireylerin çocuklarının aynı hastalığa yakalanma olasılığı % 50'dir (otozomal dominant kalıtım). Aile öyküsü her zaman olmayabilir. Hastalarında % 6-15'inde hastalık *de novo* mutasyon sonucu ortaya çıkmaktadır.

ODPKBH, 16. kromozomda yer alan *PKD1* veya 4. kromozom üzerindeki *PKD2* genlerinin birinde meydana gelen heterozigot mutasyon sonucu ortaya çıkmaktadır. Mutasyona uğramış genlerin kodladığı polikistin 1 ve 2 proteinlerinin işlevlerinin bozulmasıyla, hücre içi sinyal yolakları anormal bir işleyişe sahip olmakta ve böylece hücre büyümesi düzensizleşmekte ve sıvı salınımının artmasıyla birlikte kist oluşumu ve içinin sıvı ile dolumu meydana gelmektedir. Hastalığın başlama zamanı ve şiddetini belirleyen faktörün polikistin fonksiyonunun kritik bir eşiğin altına düşmesi olduğu düşünülmektedir.

Kaynaklar

1. Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, Kasiske BL, Odland D, Pei Y, Perrone RD, Pirson Y, Schrier RW, Torra R, Torres VE, Watnick T, Wheeler DC. Conference Participants. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2015;88 (1):17-27.
2. Ong AC, Devuyst O, Knebelmann B, Walz G. ERA-EDTA Working Group for Inherited Kidney Diseases. Autosomal dominant polycystic kidney disease: the changing face of clinical management. Lancet 2015;385:1993-2002
3. Ong AC, Harris PC. A polycystin-centric view of cyst formation and disease: the polycystins revisited. Kidney Int 2015;88:699-710
4. Balat A. Tear drops of kidney: a historical overview of Polycystic Kidney Disease. G Ital Nefrol. 2016;33: Suppl 66:33.S66.21
5. Spithoven EM, Kramer A, Meijer E, Orskov B, Wanner C, Abad JM, Aresté N, de la Torre RA, Caskey F, Couchoud C, Finne P, Heaf J, Hoitsma A, de Meester J, Pascual J, Postorino M, Ravani P, Zurriaga O, Jager KJ, Gansevoort RT; ERA-EDTA Registry; EuroCYST Consortium; WGIKD. Renal replacement therapy for autosomal dominant polycystic kidney disease (ADPKD) in Europe: prevalence and survival–an analysis of data from the ERA-EDTA Registry. Nephrol Dial Transplant. 2014;29(suppl 4):iv15-iv25
6. Willey CJ, Blais JD, Hall AK, Krasa HB, Makin AJ, Czerwiec FS. Prevalence of autosomal dominant polycystic kidney disease in the European Union. Nephrol. Dial. Transplant. 2017;32, 1356–1363
7. Harris, PC, Torres, VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. J. Clin. Invest. 2014;124: 2315–2324
8. Cornec-Le Gall E, Audrezet MP, Chen JM, Hourmant M, Morin MP, Perrichot R, Charasse C, Whebe B, Renaudineau E, Jousset P, Guillodo MP, Grall-Jezequel A, Saliou P, Ferec C, Le Meur Y: Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 2013;24: 1006–1013
9. Besse W, Dong K, Choi J, Punia S, Fedeles SV, Choi M, Gallagher AR, Huang EB, Gulati A, Knight J, Mane S, Tahvanainen E, Tahvanainen P, Sanna-Cherchi S, Lifton RP, Watnick T, Pei YP, Torres VE, Somlo S. Isolated polycystic liver disease genes define effectors of polycystin 1 function. J. Clin. Invest. 2017;127:1772–1785
10. Song, X, Haghighi, A, Iliuta, I. A, Pei, Y. Molecular diagnosis of autosomal dominant polycystic kidney disease. Expert Rev. Mol. Diagn. 2017:13: 1–11
11. Lanktree MB, Chapman AB. New reatment paradigms for ADPKD: moving towards precision medicine. Nat Rev Nephrol.2017;13(12):750-768
12. Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP,Nagao S, Rome LA, Sullivan LP, Grantham JJ. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. Kidney Int 2000;57:1460-1471

13. Nagao S, Nishii K, Yoshihara D, Kurahashi H, Nagaoka K, Yamashita T, Takahashi H, Yamaguchi T, Calvet JP, Wallace DP.Calcium channel inhibition accelerates polycystic kidney disease progression in the Cy/+ rat. Kidney Int 2008;73: 269-277
14. Wallace DP, Grantham JJ, Sullivan LP. Chloride and fluid secretion by cultured human polycystic kidney cells. Kidney Int 1996;50:1327-1336
15. Yang B, Sonawane ND, Zhao D, Somlo S, Verkman AS. Smallmolecule CFTR inhibitors slow cyst growth in polycystic kidney disease. J Am Soc Nephrol 2008;19: 1300-1310
16. Everson GT, Emmett M, Brown WR, Redmond P, Thickman D. Functional similarities of hepatic cystic and biliary epithelium: Studies of fluid constituents and in vivo secretion in response to secretin. Hepatology 1990;11:557-565
17. Pei Y, Hwang YH, Conklin J, Sundsbak JL, Heyer CM, Chan W,Wang K, He N, Rattansingh A, Atri M, Harris PC, Haider MA. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2015;26:746-753
18. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, Parfrey P, Cramer B, Coto E, Torra R, San Millan JL, Gibson R, Breuning M, Peters D, Ravine D. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009;20: 205-212
19. Cornec-Le Gall E, Audrézet MP, Rousseau A, Hourmant M, Renaudineau E, Charasse C, Morin MP, Moal MC, Dantal J, Wehbe B, Perrichot R, Frouget T, Vigneau C, Potier J, Jousset P, Guillodo MP, Siohan P, Terki N, Sawadogo T, Legrand D, Menoyo-Calonge V, Benarbia S, Besnier D, Longuet H, Férec C, Le Meur Y. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol. 2016;27, 942–951
20. Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935-1980. Am J Kidney Dis 1983;2: 630-639
21. Alan S.L. Yu, Chengli Shen, Doug Landsittel, Jared J. Grantham, Larry Cook,Vicente E. Torres, Arlene B. Chapman, Kyongtae Ty Bae, Michal Mrug,Peter C. Harris, Frederic F. Rahbari-Oskoui, Michael F. Flessner,William M. Bennett.Trajectory of the GFR in autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol. 2016;27, abstr., FR OR006
22. Schrier, R. W. ACE inhibitors, left ventricular mass and renal cyst growth in ADPKD. Pharmacol Res. 2016;114: 166–168
23. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, Grantham JJ, Harris PC, Flessner MF, Moore CG, Perrone RD. Angiotensin blockade in late autosomal dominant polycystic kidney disease. N. Engl. J. Med. 2014;371: 2267–2276
24. Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. Suppl. 2013;3: 1–150

25. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, Winklhofer FT, Brosnahan G, Czarnecki PG, Hogan MC, Miskulin DC, Rahbari-Oskoui FF, Grantham JJ, Harris PC, Flessner MF, Bae KT, Moore CG, Chapman AB.Blood pressure in early autosomal dominant polycystic kidney disease. N. Engl. J. Med. 2014;371: 2255–2266
26. Tellman, M. W., Bahler, C. D., Shumate, A. M., Bacallao, R. L., Sundaram, C. P. Management of pain in autosomal dominant polycystic kidney disease and anatomy of renal innervation. J. Urol. 2015;193:1470–1478
27. Casteleijn NF, Visser FW, Drenth JP, Gevers TJ, Groen GJ, Hogan MC, Gansevoort RT. A stepwise approach for effective management of chronic pain in autosomal- dominant polycystic kidney disease. Nephrol. Dial. Transplant. 2014;29(Suppl. 4): iv142–iv153
28. de Jager RL, Casteleijn NF, de Beus E, Bots ML, Vonken EE, Gansevoort RTBlankestijn PJ.Catheter- based renal denervation as therapy for chronic severe kidney- related pain. Nephrol. Dial. Transplant. 2017;33:614–619
29. Casteleijn NF, Blais JD, Chapman AB, Czerwiec FS, Devuyst O, Higashihara E, Leliveld AM, Ouyang J, Perrone RD, Torres VE, Gansevoort RT. Tolvaptan and kidney pain in patients with autosomal dominant polycystic kidney disease: secondary analysis from a randomized controlled trial. Am. J. Kidney Dis. 2017;69: 210–219
30. Nishiura JL, Neves RF, Eloi SR, Cintra SM, Ajzen SA, Heilberg IP.Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. Clin. J. Am. Soc. Nephrol. 2009; 4:838–844
31. Torres, V. E., Wilson, D. M., Hattery, R. R., Segura, J. W. Renal stone disease in autosomal dominant polycystic kidney disease. Am. J. Kidney Dis. 1993;22: 513–519
32. Grampsas SA, Chandhoke PS, Fan J, Glass MA, Townsend R, Johnson AM, Gabow P.Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. Am. J. Kidney Dis. 2000;36:53–57
33. Jouret F, Lhommel R, Devuyst O, Annet L, Pirson Y, Hassoun Z, Kanaan N.Diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease: attributes and limitations of the current modalities. Nephrol. Dial. Transplant. 2012;27: 3746–3751
34. Lantinga, M. A., Drenth, J. P., Gevers, T. J. Diagnostic criteria in renal and hepatic cyst infection. Nephrol. Dial. Transplant.2014;30: 744–751
35. Neuville, M., Hustinx, R., Jacques, J., Krzesinski, J. M., Jouret, F. Diagnostic algorithm in the management of acute febrile abdomen in patients with autosomal dominant polycystic kidney disease. PLOS ONE2016;11:e0161277
36. Lantinga MA, Casteleijn NF, Geudens A, de Sévaux RG, van Assen S, Leliveld AM, Gansevoort RT, Drenth JP. Management of renal cyst infection in patients with autosomal dominant polycystic kidney disease: a systematic review. Nephrol. Dial. Transplant. 2017;32(1);144–150
37. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr,Wetzel LH, BaumgartenDA, Kenney PJ,Harris PC, Klahr S, Bennett WM, HirschmanGN,

Meyers CM, Zhang X, Zhu F, Miller JP; CRISP Investigators:Volumeprogression in polycystic kidney disease. N Engl J Med2006;354: 2122–2130

38. Chapman AB, Bost JE, Torres VE, Guay-Woodford L, Bae KT, Landsittel D, Li J, King BF, Martin D, Wetzel LH, Lockhart ME, Harris PC, Moxey-Mims M, Flessner M, Bennett WM, Grantham JJ: Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol2012;7:479–486
39. Perrone RD, Mouksassi MS, Romero K, Czerwiec FS, Chapman AB, Gitomer BY, Torres VE, Miskulin DC, Broadbent S, Marier JF: Total kidney volume is a prognostic biomarker of renal function decline and progressiontoend-stage renal disease inpatients with autosomal dominant polycystic kidney disease. Kidney Int Rep2017;2: 442–450
40. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS.: TEMPO 3:4 Trial Investigators: Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med2012;367:2407–2418
41. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, Ouyang J, McQuade RD, Blais JD, Czerwiec FS, Sergeyeva O. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med 2017;377(20):1930–42
42. Gansevoort RT, Arici M, Benzing T, Birn H, Capasso G, Covic A, Devuyst O, Drechsler C, Eckardt KUEmma F, Knebelmann B, Le Meur Y, Massy ZA, Ong AC, Ortiz A, Schaefer F, Torra R, Vanholder R, Więcek A, Zoccali C, Van Biesen W. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: A position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrol Dial Transplant 2016;31:337–348
43. Irazabal MV, Rangel LJ, Bergstralh EJ, Osborn SL, Harmon AJ, Sundsbak JL, Bae KT, Chapman AB, Grantham JJ, Mrug M, Hogan MC, El-Zoghby ZM, Harris PC, Erickson BJ, King BF, Torres VE.: CRISP Investigators: Imaging classification of autosomal dominant polycystic kidney disease: A simple model for selecting patients for clinical trials. J Am Soc Nephrol2015;26:160– 172
44. Irazabal MV, Abebe KZ, Bae KT, Perrone RD, Chapman AB, Schrier RW, Yu AS, Braun WE, Steinman TI, Harris PC, Flessner MF, Torres VE.: HALT Investigators: Prognostic enrichment design in clinical trials for autosomaldominantpolycystic kidney disease: The HALT-PKD clinical trial. Nephrol Dial Transplant2017;32: 1857–1865
45. Fouad T. Chebib, Ronald D. Perrone, Arlene B. Chapman, Neera K. Dahl, Peter C. Harris ,Michal Mrug, Reem A. Mustafa, Anjay Rastogi, Terry Watnick, Alan S.L. Yu, and Vicente E. Torres. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. J Am Soc Nephrol2018;29 (10):2458-2470
46. Neijenhuis MK, Gevers TJ, Nevens F, Hogan MC, TorresVE, Kievit W, Drenth JP: Somatostatin analogues improve health-related quality of life in polycystic liver disease: A pooled analysis of two randomised, placebo-controlled trials. Aliment Pharmacol Ther 2015;42: 591–598

47. Myint, T. M., Rangan, G. K. & Webster, A. C. Treatments to slow progression of autosomal dominant polycystic kidney disease: systematic review and meta analysis of randomized trials. Nephrology 2014;19: 217–226
48. Cadnapaphornchai MA, George DM, McFann K,Wang W, Gitomer B,Strain JD, Schrier RW. Effect of pravastatin on total kidney volume, leftventricular mass index, and microalbuminuria in pediatric autosomaldominant polycystic kidney disease. Clin J Am Soc Nehrol 2014;9: 889-896
49. Freedman BS, Lam AQ, Sundsbak JL, Iatrino R, Su X, Koon SJ, Wu M, Daheron L, Harris PC, Zhou J, Bonventre JV. Reduced ciliary polycystin-2 in induced pluripotent stem cells from polycystic kidney disease patients with PKD1 mutations. J Am Soc Nephrol. 2013; 24:1571-86
50. Franchi F, Peterson KM, Xu R, Miller B, Psaltis PJ, Harris PC, Lerman LO, Rodriguez-Porcel M. Mesenchymal stromal cells improve renovascular function in polycystic kidney disease. Cell Transplant. 2015; 24:1687-98
51. Kim S, Feinberg B, Kant R, Chui B, Goldman K, Park J, Moses W, Blaha C, Iqbal Z, Chow C, Wright N, Fissell WH, Zydney A, Roy S. Dif¬fusive silicon nanopore membranes for hemodialysis applications. PLoS One. 2016;11:e0159526.
52. Fissell WH, Dubnisheva A, Eldridge AN, Fleischman AJ, Zydney AL, Roy S.High-performance silicon nanopore hemofiltration mem¬branes. J Memb Sci. 2009; 326:58-63.
53. Muthusubramaniam L, Lowe R, Fissell WH, Li L, Marchant RE, Desai TA, Roy S. Hemocompatibility of silicon-based substrates for biomedi¬cal implant applications. Ann Biomed Eng. 2011; 39:1296-305.
54. Kensinger C, Karp S, Kant R, Chui BW, Goldman K, Yeager T, Gould ER, Buck A, Laneve DC, Groszek JJ, Roy S, Fissell WH. First implantation of silicon nanopore membrane hemofilters. ASAIO J. 2016; 62:491-5