

GLOKOMDA HAYVAN MODELLERİ

49 BÖLÜM

Neşe ÇETİN DOĞAN

GİRİŞ

Glokom tüm dünyada kalıcı körlüğün önde gelen nedenlerindedir.(1) 80 milyon kadar glokom olgusu olduğu tahmin edilmekle birlikte, insidansın giderek arttığı ve 8,4 milyon glokom hastasının görme yetisini tamamen kaybedeceği düşünülmektedir.(2)

Glokom; Retina Gangliyon Hücre (RGH) kaybı ile giden ilerleyici bir nöropatidir. Hastalığın başlangıcı sinsidir. İlerleyen evrelerde görme alanı kaybı ve sonrasında körlük meydana gelir. Çoğu prelinik glokom modellemesi ,göz içinde başka yapılara zarar vermeden, sadece RGH kaybını tetikleyebilecek düzeydeki göz içi basınç artışını sağlamak üzerine planlanmıştır.(3) Ancak göz içi basıncın normal seyrettiği normotansif glokom olgularında basınçtan bağımsız çeşitli başka faktörler de mevcuttur.(4) Glokomda hayvan modelleme çalışmaları genellikle hastalığın patofizyolojisine yönelik çalışmalardır. Çünkü glokomda tanı oküler hasar ortaya çıktıktan sonra konabilmekte bu nedenle hastalığın esas başlangıcı pratikte gösterilememektedir.

Glokomu anlamak için maymun, kedi, köpek, domuz, kemirgen gibi bir çok farklı türden çeşitli hayvan modelleri kullanılmıştır(5-9). Bu modellemelerle pek çok bilgiye ulaşılmakla bir-

likte, hastalık halen tam olarak anlaşılammıştır ve tam tedavi edilememektedir.

Bir çok glokom tipi tanımlanmıştır. Kabaca, akut, kronik, primer, sekonder olarak sınıflansa da genelde insanlarda üç ana grupta incelenir. Primer Açık Açılı Glokom (PAAG), Primer Kapalı Açılı Glokom (PKAG), Primer Konjenital Glokom (PKG).(10) PAAG tüm popülasyonlarda en sık görülen glokom tipidir. Hepsinde ortak olan optik sinir atrofisi ile sonuçlanan aksomal hasardır, ancak hasara sebep olan mekanizmalar farklıdır. Artmış göz içi basıncı(GİB), çoğu tip glokomda majör risk faktörüdür ve ortak özelliğidir.

1.PRİMER AÇIK AÇILI GLOKOM:

PAAG tüm dünyada görülen en sık glokom tipidir. Bu güne kadar 20 den fazla genetik lokasyon bildirilmiş ancak 3 gen neden olarak gösterilebilmiştir. Miyosilin, Optinörin ve WDR36 genleri.(11)

Maymun (Primat): Maymunlarda glokom ilk kez 1993 yılında Porto Riko'da bulunan Cayo Santiago maymun kolonisinde tesbit edilmiştir. Rhesus maymunları gözün arka segmentindeki potansiyel hastalıklar için taranırken, tesadüfen 22 mmHg ve/ veya daha yüksek göz içi basınç-

nerasyonu ve aksonlarda kayıp görülmüştür.(85) Deneysel otoimmün glokom modelleri, immün sistemin glokomdaki rolünü göstermek için değerli çalışmalardır. Tedavi stratejilerinin belirlenmesinde de yol gösterici olabilir.

KAYNAKLAR

1. H. Quigley and A. T. Broman, "The number of people with glaucoma worldwide in 2010 and 2020," *British Journal of Ophthalmology*, vol. 90, no. 3, pp. 262–267, 2006.
2. Schmier, J.K.; Halpen, M.T.; Jones, M.L. The economic implications of glaucoma: A literature review. *Pharmacoeconomics* 2007, 25, 287–308.
3. Johnson, T.V.; Tomarev, S.I. Rodent models of glaucoma. *Brain Res. Bull.* 2010, 81, 349–358.
4. Evangelho, K.; Mogilevskaia, M.; Losada-Barragan, M.; Vargas-Sanchez, J.K. Pathophysiology of primary open-angle glaucoma from a neuroinflammatory and neurotoxicity perspective: A review of the literature. *Int. Ophthalmol.* 2017, 39, 259–271.
5. C. A. Rasmussen and P. L. Kaufman, "Primate glaucoma models," *Journal of Glaucoma*, vol. 14, no. 4, pp. 311–314, 2005.
6. J. Ruiz-Ederra, M. Garc'ia, M. Hern'andez et al., "The pig eye as a novel model of glaucoma," *Experimental Eye Research*, vol. 81, no. 5, pp. 561–569, 2005.
7. D. E. Brooks, "Glaucoma in the dog and cat," *Veterinary Clinics of North America—Small Animal Practice*, vol. 20, no. 3, pp. 775–797, 1990.
8. I. H. Pang and A. F. Clark, "Rodent models for glaucoma retinopathy and optic neuropathy," *Journal of Glaucoma*, vol. 16, no. 5, pp. 483–505, 2007.
9. U. Dietrich, "Feline glaucomas," *Clinical Techniques in Small Animal Practice*, vol. 20, no. 2, pp. 108–116, 2005.
10. H. A. Quigley, "Open-angle glaucoma," *New England Journal of Medicine*, vol. 328, no. 15, pp. 1097–1106, 1993. .
11. B. J. Fan, D. Y. Wang, D. S. C. Lam, and C. P. Pang, "Gene mapping for primary open angle glaucoma," *Clinical Biochemistry*, vol. 39, no. 3, pp. 249–258, 2006.
12. W. W. Dawson, D. E. Brooks, G. M. Hope et al., "Primary open angle glaucomas in the rhesus monkey," *British Journal of Ophthalmology*, vol. 77, no. 5, pp. 302–310, 1993.
13. D. Gaasterland and C. Kupfer, "Experimental glaucoma in the rhesus monkey," *Investigative Ophthalmology*, vol. 13, no. 6, pp. 455–457, 1974.
14. A. J. Weber and D. Zelenak, "Experimental glaucoma in the primate induced by latex microspheres," *Journal of Neuroscience Methods*, vol. 111, no. 1, pp. 39–48, 2001. .
15. H. A. Quigley and E. M. Addicks, "Chronic experimental glaucoma in primates. I. Production of elevated intraocular pressure by anterior chamber injection of autologous ghost red blood cells," *Investigative Ophthalmology and Visual Science*, vol. 19, no. 2, pp. 126–136, 1980.
16. H. A. Quigley and E. M. Addicks, "Chronic experimental glaucoma in primates. II. Effect of extended intraocular pressure elevation on optic nerve head and axonal transport," *Investigative Ophthalmology and Visual Science*, vol.19,no.2, pp. 137–152, 1980.
17. Ollivier, F.J.; Brooks, D.E.; Kallberg, M.E.; Sapp, H.L.; Komáromy, A.M.; Stevens, G.R.; Dawson, W.W.; Sherwood, M.B.; Lambrou, G.N. Time-specific diurnal intraocular pressure curves in Rhesus macaques (*Macaca mulatta*) with laser-induced ocular hypertension. *Vet. Ophthalmol.* 2004, 7, 23–27.
18. Almasieh, L.M.; Levin, L.A. Neuroprotection in glaucoma: Animal models and clinical trials. *Annu. Rev. Vis. Sci.* 2017, 3, 91–120. [CrossRef]
19. Weber, A.J.; Viswanathan, S. The primate model of experimental glaucoma. In *Mechanisms of the Glaucomas*;
20. Burgoyne, C.F. The non-human primate experimental glaucoma model. *Exp. Eye Res.* 2015, 141, 57–73.
21. Yan, Z.; Tian, Z.; Chen, H.; Deng, S.; Lin, J.; Liao, H.; Yang, X.; Ge, J.; Zhuo, Y. Analysis of a method for establishing a model with more stable chronic glaucoma in rhesus monkeys. *Exp. Eye Res.* 2015, 131, 56–62.
22. Ollivier, F.J.; Brooks, D.E.; Kallberg, M.E.; Sapp, H.L.; Komáromy, A.M.; Stevens, G.R.; Dawson, W.W.; Sherwood, M.B.; Lambrou, G.N. Time-specific diurnal intraocular pressure curves in Rhesus macaques (*Macaca mulatta*) with laser-induced ocular hypertension. *Vet. Ophthalmol.* 2004, 7, 23–27.
23. Chen, L.; Zhao, Y.; Zhang, H. Comparative anatomy of the trabecular meshwork, the optic nerve head and the inner retina in rodent and primate models used for glaucoma research. *Vision* 2016, 1, 4.
24. Almasieh, L.M.; Levin, L.A. Neuroprotection in glaucoma: Animal models and clinical trials. *Annu. Rev. Vis. Sci.* 2017, 3, 91–120.
25. Chen, L.; Zhao, Y.; Zhang, H. Comparative anatomy of the trabecular meshwork, the optic nerve head and the inner retina in rodent and primate models used for glaucoma research. *Vision* 2016, 1, 4.
26. K. N. Gelatt, G. G. Gum, and R. M. Gwin, "Animal model of human disease. Primary open angle glaucoma. Inherited primary open angle glaucoma in the beagle," *American Journal of Pathology*, vol. 102, no. 2, pp. 292–295, 1981.
27. K. Sawaguchi, Y. Nakamura, Y. Nakamura, H. Sakai, and S. Sawaguchi, "Myocilin gene expression in the trabecular meshwork of rats in a steroid-induced ocular hypertension model," *Ophthalmic Research*, vol. 37, no. 5, pp. 235–242, 2005.
28. E. Van Der Zypen, "Experimental morphological study on structure and function of the filtration angle of the rat eye," *Ophthalmologica*, vol. 174, no. 5, pp. 285–298, 1977.
29. T. Daimon, M. Kazama, Y. Miyajima, and M. Nakano, "Immunocytochemical localization of thrombomodulin in the aqueous humor passage of the rat eye," *Histochemistry and Cell Biology*, vol. 108, no. 2, pp. 121–131, 1997.

30. Ch. Reme, B. Aeberhard, and U. Urner, "The development of the chamber angle in the rat eye. Morphological characteristics of developmental stages," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 220, no. 3, pp. 139–153, 1983.
31. . P. Nucci, G. Tredici, M. P. Manitto, G. Pizzini, and R. Brancato, "Neuron-specific enolase and embryology of the trabecular meshwork of the rat eye: an immunohistochemical study," *International Journal of Biological Markers*, vol. 7, no. 4, pp. 253–255, 1992.
32. I. H. Pang, W. H. Wang, and A. F. Clark, "Acute effects of glaucoma medications on rat intraocular pressure," *Experimental Eye Research*, vol. 80, no. 2, pp. 207–214, 2005.
33. J. H. Fingert, E. M. Stone, V. C. Sheffield, and W. L. M. Alward, "Myocilin glaucoma," *Survey of Ophthalmology*, vol. 47, no. 6, pp. 547–561, 2002.
34. V. Senatorov, I. Malyukova, R. Fariss et al., "Expression of mutated mouse myocilin induces open-angle glaucoma in transgenic mice," *Journal of Neuroscience*, vol. 26, no. 46, pp. 11903–11914, 2006.
35. F. Mabuchi et al., "Optic nerve damage in mice with a targeted type I collagen mutation," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 6, pp. 1841–1845, 2004.
36. M. Aihara, J. D. Lindsey, and R. N. Weinreb, "Ocular hypertension in mice with a targeted type I collagen mutation," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 4, pp. 1581–1585, 2003.
37. C. McMahon, E. V. Semina, and B. A. Link, "Using zebrafish to study the complex genetics of glaucoma," *Comparative Biochemistry and Physiology C*, vol. 138, no. 3, pp. 343–350, 2004.
38. B. A. Link, M. P. Gray, R. S. Smith, and S. W. M. John, "Intraocular pressure in zebrafish: comparison of inbred strains and identification of a reduced melanin mutant with raised IOP," *Investigative Ophthalmology and Visual Science*, vol. 45, no. 12, pp. 4415–4422, 2004.
39. S.W.John,R.S.Smith,B.D.Perkinset al., "Characterization of the zebrafish bug eye mutation, exploring a genetic model for pressure-induced retinal cell death," *Investigative Ophthalmology & Visual Science*, vol. 44, E- Abstract 1125, 2003.
40. J. M. Stujenske, J. E. Dowling, and F. Emran, "The bug-eye mutant zebrafish exhibits visual deficits that arise with the onset of an enlarged eye phenotype," *Investigative Ophthalmology & Visual Science*, vol. 52, no. 7, pp. 4200–4207, 2011.
41. K. N. Veth, J. R. Willer, R. F. Collery et al., "Mutations in zebrafish *Lrp2* result in adult-onset ocular pathogenesis that models myopia and other risk factors for glaucoma," *PLoS Genetics*, vol. 7, no. 2, Article ID e1001310, 2011.
42. J. M. Skarie and B. A. Link, "The Primary open-angle glaucoma gene *WDR36* functions in ribosomal RNA processing and interacts with the p53 stress-response pathway," *Human Molecular Genetics*, vol. 17, no. 16, pp. 2474–2485
43. R. Jones and D. J. Rhee, "Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature," *Current Opinion in Ophthalmology*, vol. 17, no. 2, pp. 163–167, 2006.
44. J. P. Kersey and D. C. Broadway, "Corticosteroid-induced glaucoma: a review of the literature," *Eye*, vol. 20, no. 4, pp. 407–416, 2006.
45. O. A. Candia, R. Gerometta, J. C. Millar, and S. M. Podos, "Suppression of corticosteroid-induced ocular hypertension in sheep by anecortave," *Archives of Ophthalmology*, vol. 128, no. 3, pp. 338–343, 2010.
46. R. Gerometta, M. G. Spiga, T. Borr'as, and O. A. Candia, "Treatment of sheep steroid-induced ocular hypertension with a glucocorticoid-inducible MMP1 gene therapy virus," *Investigative Ophthalmology and Visual Science*, vol. 51, no. 6, pp. 3042–3048, 2010.
47. R. Gerometta, S. M. Podos, J. Danias, and O. A. Candia, "Steroid-induced ocular hypertension in normal sheep," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 2, pp. 669–673, 2009.
48. O. Y. Tektas, C. M. Hammer, J. Danias et al., "Morphologic changes in the outflow pathways of bovine eyes treated with corticosteroids," *Investigative Ophthalmology and Visual Science*, vol. 51, no. 8, pp. 4060–4066, 2010.
49. R. Gerometta, S. M. Podos, O. A. Candia et al., "Steroid-induced ocular hypertension in normal cattle," *Archives of Ophthalmology*, vol. 122, no. 10, pp. 1492–1497, 2004.
50. P. Chee and D. I. Hamasaki, "The basis for chymotrypsin-induced glaucoma," *Archives of Ophthalmology*, vol. 85, no. 1, pp. 103–106, 1971.
51. M. Best, A. Z. Rabinovitz, and S. Masket, "Experimental alphachymotrypsin glaucoma," *Annals of Ophthalmology*, vol. 7, no. 6, pp. 803–810, 1975.
52. S. Lessell and T. Kuwabara, "Experimental alpha-chymotrypsin glaucoma," *Archives of Ophthalmology*, vol. 81, no. 6, pp. 853–864, 1969.
53. C. L. Martin and M. Wyman, "Glaucoma in the Basset Hound," *Journal of the American Veterinary Medical Association*, vol. 153, no. 10, pp. 1320–1327, 1968.
54. L. G. Lovekin, "Primary Glaucoma in Dogs," *Journal of the American Veterinary Medical Association*, vol. 145, pp. 1081–1091, 1964.
55. K. N. Gelatt et al., "Clinical manifestations of inherited glaucoma in the beagle," *Investigative Ophthalmology & Visual Science*, vol. 16, no. 12, pp. 1135–1142, 1977.
56. S. Reinstein, A. Rankin, and R. Allbaugh, "Canine glaucoma: pathophysiology and diagnosis," *Compendium: Continuing Education For Veterinarians*, vol. 31, no. 10, pp. 450–453, 2009.
57. K. Fujikawa, T. Iwata, K. Inoue et al., "VAV2 and VAV3 as candidate disease genes for spontaneous glaucoma in mice and humans," *PLoS One*, vol. 5, no. 2, Article ID e9050, 2010.
58. J. C. Morrison, C. G. Moore, L. M. H. Deppmeier, B. G. Gold, C. K. Meshul, and E. C. Johnson, "A rat model of chronic pressure-induced optic nerve damage," *Experimental Eye Research*, vol. 64, no. 1, pp. 85–96, 1997.
59. R. M. Sappington et al., "The microbead occlusion model: a paradigm for induced ocular hypertension in rats and mice," *Investigative Ophthalmology & Visual Science*, vol. 51, no. 1, pp. 207–216, 2009.

60. M. C. Moreno, H. J. Aldana Marcos, J. O. Croxatto et al., "A new experimental model of glaucoma in rats through intracameral injections of hyaluronic acid," *Experimental Eye Research*, vol. 81, no. 1, pp. 71–80, 2005.
61. S. R. Shareef, E. Garcia-Valenzuela, A. Salierno, J. Walsh, and S. C. Sharma, "Chronic ocular hypertension following episcleral venous occlusion in rats," *Experimental Eye Research*, vol. 61, no. 3, pp. 379–382, 1995.
62. S. Yu, T. Tanabe, and N. Yoshimura, "A rat model of glaucoma induced by episcleral vein ligation," *Experimental Eye Research*, vol. 83, no. 4, pp. 758–770, 2006.
63. H. Levkovitch-Verbin, H. A. Quigley, K. R. G. Martin, D. Valenta, L. A. Baumrind, and M. E. Pease, "Translimbal laser photocoagulation to the trabecular meshwork as a model of glaucoma in rats," *Investigative Ophthalmology and Visual Science*, vol. 43, no. 2, pp. 402–410, 2002.
64. T. O. McDonald, J. W. Hodges, A. R. Borgmann, and F. E. Leaders, "The water-loading test in rabbits. A method to detect potential ocular hypotensive drugs.," *Archives of Ophthalmology*, vol. 82, no. 3, pp. 381–384, 1969.
65. [66] R.M.ThorpeandA.E.Kolker, "Atonographic study of water loading in rabbits.," *Archives of Ophthalmology*, vol. 77, no. 2, pp. 238–243, 1967.
66. T. Gherezghiher, W. F. March, R. E. Nordquist, and M. C. Koss, "Laser-induced glaucoma in rabbits," *Experimental Eye Research*, vol. 43, no. 6, pp. 885–894, 1986.
67. B. Johnson, P. House, W. Morgan, X. Sun, and D. Y. Yu, "Developing laser-induced glaucoma in rabbits," *Australian and New Zealand Journal of Ophthalmology*, vol. 27, no. 3-4, pp. 180–183, 1999.
68. C. V. Schloesser, "Acutes Secundar-Glaucom beim Kaninchen," *Zeitschrift für Vergleichende Augenheilkunde*, vol. 35, no. 4, pp. 232–233, 1886.
69. R. R. Fox, D. D. Crary, E. J. Babino, and B. Sheppard, "Buphthalmia in the rabbit: pleiotropic effects of the (bu) gene and a possible explanation of mode of gene action," *Journal of Heredity*, vol. 60, no. 4, pp. 206–212, 1969.
70. B. L. Hanna, P. B. Sawin, and L. B. Sheppard, "Recessive buphthalmos in the rabbit," *Genetics*, vol. 47, pp. 519–529, 1962.
71. A. E. Kolker, R. A. Moses, M. A. Constant, and B. Becker, "The development of glaucoma in rabbits," *Investigative ophthalmology*, vol. 2, pp. 316–321, 1963.
72. [80] E. C. G. M. Hampson, R. I. E. Smith, and M. E. Bernays, "Primary glaucoma in Burmese cats," *Australian Veterinary Journal*, vol. 80, no. 11, pp. 672–680, 2002.
73. K. N. Gelatt, G. G. Gum, and R. M. Gwin, "Animal model of human disease. Primary open angle glaucoma. Inherited primary open angle glaucoma in the beagle," *American Journal of Pathology*, vol. 102, no. 2, pp. 292–295, 1981.
74. G.J.McLellan, D.M.Betts,K.Sigle,andS.Grozdanic, "Congenital glaucoma in the siamese cat—a novel spontaneous animal model for glaucoma research," *Investigative Ophthalmology & Visual Science*, vol. 46: E-Abstract 134, 1995.
75. S. Jacobi and R. R. Dubielzig, "Feline primary open angle glaucoma," *Veterinary Ophthalmology*, vol. 11, no. 3, pp. 162–165, 2008
76. W. H. F. Addison and H. W. How, "Congenital hypertrophy of the eye in an albino rat," *The Anatomical Record*, vol. 32, no. 4, pp. 271–277, 1926.
77. C. Young, M. F. W. Festing, and K. C. Barnett, "Buphthalmos (congenital glaucoma) in the rat," *Laboratory Animals*, vol. 8, no. 1, pp. 21–31, 1974.
78. Z. Gatziofufas, P. Charalambous, B. Seitz et al., "Cholinergic inhibition by botulinum toxin in a rat model of congenital glaucoma raises intraocular pressure," *British Journal of Ophthalmology*, vol. 92, no. 6, pp. 826–831, 2008.
79. [113] M. B. Wax, "The case for autoimmunity in glaucoma," *Experimental Eye Research*, vol. 93, no. 2, pp. 187–190, 2010.
80. [114] J. Caprioli and A. L. Coleman, "Blood pressure, perfusion pressure, and glaucoma," *American Journal of Ophthalmology*, vol. 149, no. 5, pp. 704–712, 2010.
81. [115] M.B.Shields, "Normal-tension glaucoma: is it different from primary open-angle glaucoma?" *Current Opinion in Ophthalmology*, vol. 19, no. 2, pp. 85–88, 2008
82. [118] S. W. John and al. et, "Essential iris atrophy, pigment dispersion, and glaucoma in DBA/2J mice," *Investigative Ophthalmology&VisualScience*, vol. 39, no. 6, pp. 951–962, 1998.
83. B. Chang, R. S. Smith, N. L. Hawes et al., "Interacting loci cause severe iris atrophy and glaucoma in DBA/2J mice," *Nature Genetics*, vol. 21, no. 4, pp. 405–409, 1999.
84. M. G. Anderson, R. S. Smith, N. L. Hawes et al., "Mutations in genes encoding melanosomal proteins cause pigmentary glaucoma in DBA/2J mice," *Nature Genetics*, vol. 30, no. 1, pp. 81–85, 2002.
85. M. B. Wax, G. Tezel, J. Yang et al., "Induced autoimmunity to heat shock proteins elicits glaucomatous loss of retinal ganglion cell neurons via activated T-cell-derived Fas-ligand," *Journal of Neuroscience*, vol. 28, no. 46, pp. 12085–12096, 2008.