

# Bölüm

## 18

# HEMORAJİK İNME

İrem İLGEZDİ<sup>1</sup>

### GİRİŞ

Intraserebral hemoraji (İSH), herhangi bir travma öyküsü olmaksızın beyin parankiminde meydana gelen kanamalardır. İskemik inmelerden çok daha az sıklıkta görülmeye rağmen, daha mortal seyretmesi nedeni ile risk faktörlerini tanımlamak, primer ve sekonder koruyucu yaklaşımalarını uygulayabilmek, hemoraji tedavisini yönetebilmek oldukça önemlidir. Bu bölümde İSH epidemiyolojisi, patofizyolojisi, oluşum mekanizmaları, kliniği ve tedavi yaklaşımı üzerinde durulacaktır.

### Epidemiyoloji

İSH tüm inmelerin yaklaşık %10-20'sini oluşturur (1). Sık görülmesi ve mortalite oranının %50'ye varması nedeni ile önemli bir antitedir (2). Yirmi iki ülkeden 3000 hastanın alındığı INTERSTROKE çalışmasında hastaların %22'inde İSH tanısı konulurken, en yüksek Afrikali, güney Amerikalı ve güney doğu Asyalı hastalarda saptanmıştır (1). Otuz altı çalışmanın derlendiği bir sistematik derlemede, İSH insidansı 24,6/100.000 saptanırken özellikle güney ve doğu Asya'da insidansın yüksek olduğu gözlenmiştir (3). Tüm yaş gruplarında insidansı erkeklerde daha yüksektir (4). Diğer inme tiplerinde olduğu gibi İSH görme sıklığı da yaşla birlikte artar. Fransa'da yapılan bir çalışmada 1985 ve 2008 yıllarındaki İSH vakaları gözden geçirildiğinde < 60 yaş insidansı %50

azalırken, 75 yaş ≤ %80 artmaktadır. Bu insidans artışının özellikle lober hemorajiler yönünde ve antitrombotik kullanım artışı ile ilişkili olduğu gözlenmiştir (5). Genetik çalışmalar serebrovasküler hastalıklar içerisinde daha çok iskemik serebrovasküler hastalıklar üzerinde yoğunlaşmıştır. Albert ve arkadaşlarının yaptığı çalışmada İSH hastalarında ailesel birikim olabileceği belirtilmiştir (6). Çin'de yapılan bir çalışmada 14q22-q23 kromozomunda PRKCH geninde 1425G/A tek nükleotid polimorfizmi varlığında İSH insidansının arttığı belirtilmiştir (7). Anjiotensin dönüştürücü enzim (ACE) gen polimorfizminin de İSH riskini artırdığı düşünülmektedir (8). Tip IV kollojen a1'i (COL4A1) kodlayan gende mutasyon serebral mikrokanamalara ve sporadik İSH'a yatkınlık oluşturabilir (9-11).

### Patofizyoloji

1868 yılında Charcot ve Bouchard hipertansif İSH hastalarının beyin dokusunda 'milier anevrizmaları' tanımlanmıştır. Yirminci yüzyıl başlarında Ellis İSH patogenezinde primer olarak intimal lezyonun ortaya çıktığını, eşlik eden media ve adventisyaya tutulumunun da olabileceğini sonuç olarak vasküler duvara kan geçişini ve disseke anevrizmaların, bu vasküler anomaliler nedeni ile de rüptür ve hemorajilerin ortaya çıkabileceğini öne sürmüştür (12). Ross Russell tarafından da milier anevrizma-

<sup>1</sup> Dr. Öğr. Üyesi İrem İlgezdi Giresun Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı, iremilgezdi@yahoo.com

## KAYNAKLAR

1. O'Donnell, M.J., Xavier, D., Liu, L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study, Lancet, 2010;376:112-123.
2. Kase CS ve Shoamanesh A. (2016) Intracerebral Hemorrhage, Bradley's Neurology in Clinical Practice, 7th edit; 66:968-982. London, New York, Oxford, Philadelphia, St Louis, Sydney, Toronto, Elsevier Inc.
3. van Asch, CJ, Luitse, MJ, Rinkel , GJ., Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis., Lancet Neurol , 2010;9:167.
4. Jolink W, Klijn C., Brouwers P. et al. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage., Neurology, 2015;85:1318-1324.
5. Bejot, Y., Cordonnier, C., Durier, J. et al. Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study, Brain, 2013;136:658.
6. Alberts M., McCarron M., Hoffman K. et al. Familial clustering of intracerebral hemorrhage: A prospective study in North Carolina., Neuroepidemiology, 2002;21:18.
7. Wu, L, Shen, Y., Liu, X. et al. The 1425G/A SNP in PRKCH is associated with ischemic stroke and cerebral hemorrhage in a Chinese population., Stroke, 2009;40:2973.
8. Sun Y., Liu Y., Watts L. et al. Genetic Associations of Angiotensin- Converting Enzyme with Primary Intracerebral Hemorrhage: A Meta-analysis., PLoS ONE, 2013;8:e67402.
9. Gould D., Phalan F., van Mil S. et al. Role of COL4A1 in small-vessel disease and hemorrhagic stroke, N Engl J Med, 2006;354:1489.
10. Lanfranconi S., Markus H., COL4A1 mutations as a monogenic cause of cerebral small vessel disease: a systematic review., Stroke, 2010;41:e513.
11. Weng Y., Sonni A., Labelle-Dumais C. et al. COL4A1 mutations in patients with sporadic late-onset intracerebral hemorrhage, Ann Neurol, 2012;71:470.
12. Ellis A., The pathogenesis of spontaneous cerebral hemorrhage., Proc Pathol Soc, 1909;12:197.
13. Ross Russell R., Observations on intracerebral aneurysms., Brain, 1963;86:425.
14. Fisher C., Cerebral miliary aneurysms in hypertension., Am J Pathol, 1972;66:313.
15. Wang J., Preclinical and clinical research on inflammation after intracerebral hemorrhage., Prog Neurobiol, 2010;92:463.
16. Ziai W., Hematology and inflammatory signaling of intracerebral hemorrhage., Stroke, 2013;44:S74.
17. Bekelis K., Desai A., Zhao W. et al. Computed tomography angiography: improving diagnostic yield and cost effectiveness in the initial evaluation of spontaneous nonsubarachnoid intracerebral hemorrhage., J Neurosurg., 2012;117:761-766.
18. Delgado Almundo J., Schaefer P., Forero N. et al. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage., AJNR Am J Neuroradiol., 2009;30:1213-1221.
19. Hemphill J., Greenberg S., Anderson C et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, Stroke, 2015;46:3023-2060.
20. Al-Shahi Salman R., Hall J., Horne M. et al. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study., Lancet Neurol., 2012;11:217-224.
21. Flemming K., Link M., Christianson T. et al. Prospective hemorrhage risk of intracerebral cavernous malformations., Neurology, 2012;78:632-636.
22. Lovelock C., Cordonnier C., Naka H. et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies., Stroke, 2010;41:1422-1428.
23. Ruff C., Giugliano R., Braunwald E. et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials., Lancet, 2014;383:955-962.
24. Lopes R., Guimaraes P., Kolls B. et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anti-coagulation therapy., Blood, 2017;129:2980-2987.
25. National Institute of Neurological Diseases and Stroke (NINDS) rtPA Stroke Study Group, Tissue plasminogen activator for acute ischemic stroke., N. Engl. J. Med., 1995;333:1581-1587.
26. National Institute of Neurological Diseases and Stroke (NINDS) tPA Stroke Study Group, Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke., Stroke, 1997;28:2109-2118.
27. Dannenberg S., Scheitz J., Rozanski M. et al. Number of cerebral microbleeds and risk of intracerebral hemorrhage after intravenous thrombolysis., Stroke, 2014;45:2900-2905.
28. Diedler J., Ahmed N., Sykora M. et al. Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset., Stroke, 2010;41:288-294.
29. Poppe A., Majumdar S., Jeerakathil T. et al. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis., Diabetes Care, 2009;32:617-622.
30. Butcher K., Jeerakathil T., Hill M. et al. ICH ADAPT Investigators., The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial., Stroke, 2013;44:620-626.
31. Kase C., Shoamanesh A., Greenberg S. et al.(2016) Intracerebral Hemorrhage. Kase CS, Shoamanesh A., Greenberg S.M, Caplan L.R. Stroke: Pathophysiology, Diagnosis, and Management, 6th ed.;28:466-515. Elsevier Inc.
32. Martin-Schild S., Albright K., Hallevi H. et al. Intracerebral hemorrhage in cocaine users., Stroke, 2010;41:680.
33. Terruso V., D'Amelio M., Di Benedetto N. et al. Frequency and determinants for hemorrhagic transformation of cerebral infarction., Neuroepidemiology, 2009;33:261.
34. Alvarez-Sabin J., Maisterra O., Santamarina E. et al. Factors influencing haemorrhagic transformation in ischaemic stroke., Lancet Neurol, 2013;12:689.
35. Leira R., Sobrino T., Blanco M. et al. A higher body temperature is associated with haemorrhagic transformation in patients with acute stroke untreated with recom-

- binant tissue-type plasminogen activator (rtPA), Clin Sci., 2012;122:113.
36. Öcek L., Guner D., Uludag I. et al. Factors for Hemorrhagic Transformation in Patients with Acute Middle Cerebral Artery Infarction, Noro Psikiyatr Ars., 2015;52:342-345.
  37. Demirtas B., Öcek L., Zorlu Y. et al. Factors Associated With Hemorrhagic Transformation in Infarctions Involving the Posterior Circulation System., Journal of Stroke and Cerebrovascular Diseases, 2019;28:2193-2200.
  38. Fiorelli M., Bastianello S., von Kummer R. et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort., Stroke, 1999;30:2280.
  39. Kase C., Greenberg S., Mohr J. et al.(2011), Stroke: Pathophysiology, Diagnosis and Management. Mohr J.P., Wolf P.A., Grotta J.C. et al. (Ed.).Intracerebral hemorrhage. Philadelphia, Elsevier Saunders.
  40. Kase C.S (2010) Clinical presentation of intracerebral hemorrhage. Carhuapoma J.R., Mayer S.A., Hanley D.H. (Ed.), Intracerebral Hemorrhage. Cambridge , Cambridge Medicine.
  41. Flint A., Roebken A., Singh V., Primary intraventricular hemorrhage: yield of diagnostic angiography and clinical outcome., Neurocrit., 2008;Care 8:330-336.
  42. Chalela J., Kidwell C., Nentwich L. et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison., Lancet, 2007;369:293-298.
  43. Macellari F., Paciaroni M., Agnelli G. et al. Neuroimaging in intracerebral hemorrhage., Stroke, 2014;45:903-908.
  44. Davis S., Broderick J., Hennerici M. et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage., Neurology, 2006;66:1175-1181.
  45. Veltkamp R., Purrucker J., Management of Spontaneous Intracerebral Hemorrhage., Current Neurology and Neuroscience Reports, 2017;17
  46. Demchuk A., Dowlatshahi D., Rodriguez-Luna D. PREDICT/Sunnybrook ICH CTA Study Group., Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study.Lancet Neurol., 2012;11:307-314.
  47. Rizos T., Dörner N., Jenetzky E. et al. Spot signs in intracerebral hemorrhage: useful for identifying patients at risk for hematoma enlargement?, Cerebrovasc Dis., 2013;35:582-589.
  48. Romero J., Brouwers H., Lu J. et al. Prospective validation of the computed tomographic angiography spot sign score for intracerebral hemorrhage., Stroke, 2013;44:3097.
  49. Thompson A., Kosior J., Gladstone D. et al. Defining the CT angiography "spot sign" in primary intracerebral hemorrhage., Can J Neurol Sci., 2009;36:456.
  50. Huynh T., Demchuk A., Dowlatshahi D. et al. PREDICT/ Sunnybrook ICH CTA Study Group. , Spot sign number is the most important spot sign characteristic for predicting hematoma expansion using first-pass computed tomography angiography: analysis from the PREDICT study., Stroke, 2013;44:972-977.
  51. Smith E., Shobha N., Dai D. et al. A risk score for in-hospital death in patients admitted with ischemic or hemorrhagic stroke., J Am Heart Assoc., 2013;2:e005207.
  52. Garrett J., Zarghouni M., Layton K., et al. Validation of clinical prediction scores in patients with primary intracerebral hemorrhage., Neurocrit Care., 2013;19:329-335.
  53. Hemphill J. 3., Bonovich D., Besmertis L. et al. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage., Stroke, 2001;32:891-897.
  54. Steiner T., Rosand J., Diringer M., Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions., Stroke, 2006;37:256-262.
  55. Dentali F., Ageno W., Crowther M., Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms., J Thromb Haemost., 2006;4:1853-1863.
  56. Sarode R., Milling T. J. J., Refaai M. et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIb study., Circulation., 2013;128:1234-1243.
  57. Andrews C., Jauch E., Hemphill J. 3. et al. Emergency neurological life support: intracerebral hemorrhage., Neurocrit Care., 2012;17:S37-S46.
  58. Chatterjee S., Sardar P., Biondi-Zocca G. et al. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation., JAMA Neurol, 2013;70:1486-1490.
  59. Christensen H., Cordonnier C., Körv J., et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage., European Stroke Journal, 2019.
  60. Ansell J., Bakhru S., Laulicht B. et al. Use of PER977 to reverse the anticoagulant effect of edoxaban., N Engl J Med., 2014;371:2141-2142.
  61. Baharoglu M., Cordonnier C., Al-Shahi Salman R. et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial.Lancet. 2016;25-387:2605-2613.
  62. Zazulia A., Diringer M., Videen T. et al. Hypoperfusion without ischemia surrounding acute intracerebral hemorrhage., J Cereb Blood Flow Metab., 2001;21:804-810.
  63. Sakamoto Y., Koga M., Yamagami H. et al. SAMURAI Study Investigators. , Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: The Stroke Acute Management With Urgent Risk- Factor Assessment and Improvement-Intracerebral Hemorrhage Study., Stroke, 2013;44:1846-1851.
  64. Arima H., Anderson C., Wang J. et al. Intensive Blood Pressure Reduction in Acute Cerebral Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage., Hypertension., 2010;56:852-858.

65. Anderson C., Heeley E., Huang Y. et al. INTERACT2 Investigators. , Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage., *N Engl J Med.*, 2013;368:2355-2365.
66. Qureshi A., Palesch Y., Martin R. et al. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study., *Arch Neurol.*, 2010;67:570-576.
67. Qureshi A., Palesch Y., Barsan W. et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage., *N Engl J Med.*, 2016;375:1033-1043.
68. Kimura K., Iguchi Y., Inoue T. et al. Hyperglycemia independently increases the risk of early death in acute spontaneous intracerebral hemorrhage., *J Neurol Sci.*, 2007;255:90-94.
69. Stead L., Gilmore R., Bellolio M. et al. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke., *Neurocrit Care.*, 2009;10:181-186.
70. Finfer S., Chittock D., Su S. et al. NICE-SUGAR Study Investigators. , Intensive versus conventional glucose control in critically ill patients., *N Engl J Med.*, 2009;360:1283-1297.
71. Fingas M., Penner M., Silasi G. et al. Treatment of intracerebral hemorrhage in rats with 12 h, 3 days and 6 days of selective brain hypothermia., *Exp Neurol.*, 2009;219:156-162.
72. Kollmar R., Staykov D., Dörfler A. et al. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage., *Stroke*, 2010;41:1684-1689.
73. Beghi E., D'Alessandro R., Beretta S. et al. Epistroke Group. Incidence and predictors of acute symptomatic seizures after stroke., *Neurology*, 2011;77:1785-1793.
74. De Herdt V., Dumont F., Hénon H. et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome., *Neurology*, 2011;77:1794-1800.
75. Arntz R., Rutten-Jacobs L., Maaijwee N. et al. Post-stroke epilepsy in young adults: a long-term follow-up study., *PLoS One*, 2013;8:e55498.
76. The CLOTS (Clots in Legs Or stockings after Stroke) Trial Collaboration, Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial [published correction appears in Ann Intern Med. 2010;153:851]., *Ann Intern Med.*, 2010;153:553-562.
77. Dennis M., Sandercock P., Reid J. et al. CLOTS Trial Collaboration. , Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial., *Lancet*, 2009;373:1958-1965.
78. Dennis M., Sandercock P., Reid J. et al. CLOTS (Clots in Legs Or stockings after Stroke) Tr, Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*. 2013;382:516-524.
79. Dennis M., Sandercock P., Reid J. et al. CLOTS Trials Collaboration. , The effect of graduated compres-
- sion stockings on long-term outcomes after stroke: the CLOTS trials 1 and 2., *Stroke*, 2013;44:1075-1079.
80. Paciaroni M., Agnelli G., Venti M. et al. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies., *J Thromb Haemost.*, 2011;9:893-898.
81. Mendelow A., Gregson B., Fernandes H. et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomized trial., *Lancet*, 2005;365:387-397.
82. Mendelow A., Gregson B., Rowan E. et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial., *Lancet*, 2013;382:397-408.
83. Bhattathiri P., Gregson B., Prasad K. et al. STICH Investigators. , Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial., *Acta Neurochir Suppl.*, 2006;96:65-68.
84. Hallevi H., Albright K., Aronowski J. et al. Intraventricular hemorrhage: anatomic relationships and clinical implications., *Neurology*, 2008;70:848-852.
85. Huttner H., Hartmann M., hrmann M. K. et al. Repeated digital subtraction angiography after perimesencephalic subarachnoid hemorrhage?, *J Neuroradiol*, 2006;33:87-89.
86. Webb A., Ullman N., Mann S. et al. Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) program., *Stroke*, 2012;43:1666-1668.
87. Yadav Y., Mukerji G., Shenoy R. et al. Endoscopic management of hypertensive intraventricular hemorrhage with obstructive hydrocephalus., *BMC Neurol*, 2007;7:1.
88. Zhang Z., Li X., Liu Y. et al. Application of neuroendoscopy in the treatment of intraventricular hemorrhage., *Cerebrovasc Dis.*, 2007;24:91-96.
89. Mayer S., Brun N., Begtrup K. et al. Recombinant activated factor VII for acute intracerebral hemorrhage., *N Engl J Med.*, 2005;352:777-785.
90. Mayer S., Brun N., Begtrup K. et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage., *N Engl J Med.*, 2008;358:2127-2137.
91. Spragg N., Flaherty K., Appleton J. et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial., *Lancet*, 2018;2107-2115391.
92. McKinney J., Kostis W., Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials., *Stroke*, 2012;43:2149-2156.
93. Majeed A., Kim Y., Roberts R. et al. Optimal timing of resumption of warfarin after intracranial hemorrhage., *Stroke*, 2010;41:2860-2866.
94. Sansing L., Messe S., Cucchiara B. et al. CHANT Investigators. , Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH., *Neurology*, 2009;72:1397-1402.