BÖLÜM 15

NÖROMETABOLİK HASTALIKLARDA KÖK HÜCRE, ENZİM REPLASMAN TEDAVİSİ VE BİREYSEL TEDAVİ SEÇENEKLERİ

Aliye GÜLBAHÇE [1]
Fatih KARDAŞ [2]

LİZOZOMAL DEPO HASTALIKLARI

Giriş

Lizozomlar

Lizozomlar glikozaminoglikan, sfingolipid, glikojen, proteinler gibi birçok molekülün metabolize edilmesini ve geri dönüşümünü düzenleyen hücre içi bir organeldir. Bu katabolik süreçler 60 farklı asidik hidrolaz enziminin (glikozidazlar, sülfatazlar, peptidazlar vb) düzen içinde çalışması ile gerçekleşir. [1]

Lizozomal enzimler ve diğer protein yapılar ribozomlarda sentezlendikten sonra endoplazmik retikuluma (ER) taşınır. ER'da katlanan proteinler son değişiklikler yapılmak üzere golgi'ye aktarılır. Geç golgideki modifikasyonlardan sonra bazı proteinlere mannoz 6 fosfat reseptörleri eklenir ve tüm aşamalar tamamlanarak lizozomlara ulaşmak üzere golgi'den tomurcuklanarak ayrılır. Substratlar lizozomların içine fagositoz, makropinositoz, klatrin aracılı endositoz, caveolin aracılı endositoz ve klatrin ve caveolin bağımsız endositoz gibi substratın yapısına uygun bir yöntem ile taşınmaktadır. Lizozom içine molekülün girişi mannoz 6 fosfat reseptörleri veya membranda bulunan integral proteinler aracılığı ile sağlanmaktadır. Tüm basamaklardan herhangi birindeki sorun sistemin çalışmasında aksaklıklara neden olarak farklı klinik tabloları oluşturur.[1,2]

Lizozomal Depo Hastalıkları

Lizozomal fonksiyon için gerekli asidik hidrolazlar, integral membranda taşıyıcı proteinlerin veya lizozomal olmayan proteinlerin eksikliği sonucu lizozomlarda glikozaminoglikan, glikojen, oligosakkarit gibi yapıların birikmesi sonucu çoklu organ disfonksiyonuna neden olan depo hastalıklarıdır.[1]

Substratlar öncelikle endozom ve lizozomda depolanmaya başlar, ilerleyen dönemde tüm hücre içi bölmelerde ve hücre dışı alanda birikerek hücre ve doku disfonksiyonuna neden olur. Artan oksidatif stres ve lokal inflamasyon dolaylı olarak özellikle merkezi sinir sisteminde olmak üzere hasara neden olabilir. [2]

Prenatal dönemde fetal hidrops olarak bulgu verebildiği gibi, ilerleyen yaş ile artan birikime bağlı multipl sistemik tutulum ile seyredebilen geniş klinik spektrumda hastalıklardır. Farklı substrat birikimleri benzer fenotipte hastalıklara neden olabilmektedir. Çok sayıdaki lizozomal

[1] Uzm. Dr., Kocaeli Şehir Hastanesi, Çocuk Metabolizma Hastalıkları, aliyegulbahcedr@gmail.com, ORCID iD: 0000-0003-0894-4447
[2] Prof. Dr., Erciyes Üniversitesi, Tıp Fakültesi, Dahili Tıp Bilimleri Bölümü, Çocuk Sağlığı ve Hastalıkları AD., fkardas@erciyes.edu.tr, ORCID iD: 0000-0002-2276-7611

KAYNAKLAR

1. Parenti G, Andria G, Valenzano KJ. Pharmacological Chaperone Therapy: Preclinical Development, Clinical Translation, and Prospects for the Treatment of Lysosomal Storage Disorders. Mol Ther. 2015;23(7):1138-48.
2. Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Annu Rev Med. 2015;66:471-86.
3. Beck M. Treatment strategies for lysosomal storage disorders. Dev Med Child Neurol. 2018;60(1):13-8.
4. Roberto Giugliani IN, Steven Chen, William Pardridge, Patrice Rioux. Intravenous infusion of iduronidase-IgG and its impact on the central nervous system in children with Hurler syndrome. Molecular Genetics and Metabolism. 2017;120(1):S55-S6.
5. Naumchik BM, Gupta A, Flanagan-Steet H, et al. The Role of Hematopoietic Cell Transplant in the Glycoprotein Diseases. Cells. 2020;9(6).
6. Mohamed FE, Al-Gazali L, Al-Jasmi F, Ali BR. Pharmaceutical Chaperones and Proteostasis Regulators in the Therapy of Lysosomal Storage Disorders: Current Perspective and Future Promises. Front Pharmacol. 2017;8:448.
7. Platt FM, Jeyakumar M. Substrate reduction therapy. Acta Paediatr. 2008;97(457):88-93.
8. Smid BE, Ferraz MJ, Verhoek M, et al. Biochemical response to substrate reduction therapy versus enzyme replacement therapy in Gaucher disease type 1 patients. Orphanet J Rare Dis. 2016;11:28.
9. Biffi A. Hematopoietic Stem Cell Gene Therapy for Storage Disease: Current and New Indications. Mol Ther. 2017;25(5):1155-62.
10. Rossini L, Durante C, Marzollo A, Biffi A. New Indications for Hematopoietic Stem Cell Gene Therapy in Lysosomal Storage Disorders. Front Oncol. 2022;12:885639.
11. de Castro MJ, Del Toro M, Giugliani R, Couce ML. Gene Therapy for Neuronopathic Mucopolysaccharidoses: State of the Art. Int J Mol Sci. 2021;22(17).
12. Gentner B, Tucci F, Galimberti S, et al. Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome. N Engl J Med. 2021;385(21):1929-40.
13. Cherqui S. Hematopoietic Stem Cell Gene Therapy for Cystinosis: From Bench-to-Bedside. Cells. 2021;10(12).
14. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16.
15. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50.
16. Groenen AG, La Rose AM, Li M, et al. Elevated granulocyte-colony stimulating factor and hematopoietic stem cell mobilization in Niemann-Pick type C1 disease. J Lipid Res. 2022;63(2):100167.
17. Marie T. Vanier CC, and Thierry Levade. Disorders of Sphingolipid Synthesis, Sphingolipidoses, Niemann-Pick Disease Type C and Neuronal Ceroid Lipofuscinoses. In: Jean-Marie Saudubray MRB, Ángeles García-Cazorla, John Walter, editor. Inborn Metabolic Diseases Diagnosis and Treatment2022. p. 755-7.
18. Patterson MC, Mengel E, Wijburg FA, et al. Disease and patient characteristics in NP-C patients: findings from an international disease registry. Orphanet J Rare Dis. 2013;8:12.
19. Modin L, Ng V, Gissen P, et al. A Case Series on Genotype and Outcome of Liver Transplantation in Children with Niemann-Pick Disease Type C. Children (Basel). 2021;8(9).
20. Reiner Z. Resistance and intolerance to statins. Nutr Metab Cardiovasc Dis. 2014;24(10):1057-66.
21. Pineda M, Walterfang M, Patterson MC. Miglustat in Niemann-Pick disease type C patients: a review. Orphanet J Rare Dis. 2018;13(1):140.
22. Patterson MC, Di Bisceglie AM, Higgins JJ, et al. The effect of cholesterol-lowering agents on hepatic and plasma cholesterol in Niemann-Pick disease type C. Neurology. 1993;43(1):61-4.
23. Vite CH, Bagel JH, Swain GP, et al. Intracisternal cyclodextrin prevents cerebellar dysfunction and Purkinje cell death in feline Niemann-Pick type C1 disease. Sci Transl Med. 2015;7(276):276ra26.
24. Benatar M, Wuu J, Andersen PM, et al. Randomized, double-blind, placebo-controlled trial of arimoclomol in rapidly progressive SOD1 ALS. Neurology. 2018;90(7):e565-e74.
25. Cougnoux A, Yerger JC, Fellmeth M, et al. Reduction of glutamate neurotoxicity: A novel therapeutic approach for Niemann-Pick disease, type C1. Mol Genet Metab. 2021;134(4):330-6.
26. Bonney DK, O'Meara A, Shabani A, et al. Successful allogeneic bone marrow transplant for Niemann-Pick disease type C2 is likely to be associated with a severe 'graft versus substrate' effect. J Inherit Metab Dis. 2010;33 Suppl 3:S171-3.
27. Bae JS, Furuya S, Ahn SJ, Yi SJ, Hirabayashi Y, Jin HK. Neuroglial activation in Niemann-Pick Type C mice is suppressed by intracerebral transplantation of bone marrow-derived mesenchymal stem cells. Neurosci Lett. 2005;381(3):234-6.
28. Kurokawa Y, Osaka H, Kouga T, et al. Gene Therapy in a Mouse Model of Niemann-Pick Disease Type C1. Hum Gene Ther. 2021;32(11-12):589-98.
29. Imanaka T. [Biogenesis, the Function of Peroxisomes, and Their Role in Genetic Disease: With a Focus on the ABC Transporter]. Yakugaku Zasshi. 2018;138(8):1067-83.
30. McGuinness MC, Wei H, Smith KD. Therapeutic developments in peroxisome biogenesis disorders. Expert Opin Investig Drugs. 2000;9(9):1985-92.
31. Moser HW, Moser AB, Hollandsworth K, Brereton NH, Raymond GV. "Lorenzo's oil" therapy for X-linked adrenoleukodystrophy: rationale and current assessment of efficacy. J Mol Neurosci. 2007;33(1):105-13.
32. Yu J, Chen T, Guo X, et al. The Role of Oxidative Stress and Inflammation in X-Link Adrenoleukodystrophy. Front Nutr. 2022;9:864358.
33. Turk BR, Nemeth CL, Marx JS, et al. Dendrimer-N-acetyl-L-cysteine modulates monophagocytic response in adrenoleukodystrophy. Ann Neurol. 2018;84(3):452-62.

34. Aubourg P, Blanche S, Jambaque I, et al. Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. N Engl J Med. 1990;322(26):1860-6.
35. Peters C, Charnas LR, Tan Y, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. 2004;104(3):881-8.
36. Cartier N, Aubourg P. Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. Brain Pathol. 2010;20(4):857-62.
37. Cartier N, Hacein-Bey-Abina S, Bartholomae CC, et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. Science. 2009;326(5954):818-23.
38. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. 2017;377(17):1630-8.
39. Klouwer FC, Berendse K, Ferdinandusse S, Wanders RJ, Engelen M, Poll-The BT. Zellweger spectrum disorders: clinical overview and management approach. Orphanet J Rare Dis. 2015;10:151.
40. Enns GM, Ammous Z, Himes RW, et al. Diagnostic challenges and disease management in patients with a mild Zellweger spectrum disorder phenotype. Mol Genet Metab. 2021;134(3):217-22.
41. Alhazmi HH. Renal oxalate stones in children with Zellweger spectrum disorders. Saudi J Anaesth. 2018;12(2):332-4.
42. Klouwer FCC, Koot BGP, Berendse K, et al. The cholic acid extension study in Zellweger spectrum disorders: Results and implications for therapy. J Inherit Metab Dis. 2019;42(2):303-12.
43. Chen K, Zhang N, Shao JB, et al. Allogeneic Hematopoietic Stem Cell Transplantation for PEX1-Related Zellweger Spectrum Disorder: A Case Report and Literature Review. Front Pediatr. 2021;9:672187.
44. Van Maldergem L, Moser AB, Vincent MF, et al. Orthotopic liver transplantation from a living-related donor in an infant with a peroxisome biogenesis defect of the infantile Refsum disease type. J Inherit Metab Dis. 2005;28(4):593-600.
45. Argyriou C, Polosa A, Song JY, et al. AAV-mediated PEX1 gene augmentation improves visual function in the PEX1-Gly844Asp mouse model for mild Zellweger spectrum disorder. Mol Ther Methods Clin Dev. 2021;23:225-40.