25.
BÖLÜM

SIK GÖRÜLEN GENETİK SENDROMLARDA OTOİMMUN TİROİD HASTALIKLARI

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GİRİŞ

Otoimmün tiroid hastalığı (OTH), çocuk ve ergenlerde en sık görülen tiroid patolojisidir. OTH; genellikle HashimotoTiroiditi (HT) ve Graves Hastalığı (GH) olmak üzere iki ana başlıkta değerlendirilir. OTH genetik, çevresel ve endojen faktörler arasındaki etkileşimden kaynaklanır. Hem hücresel hem de humoral immün yanıtlar patogenezde rol oynamaktadır. OTH'da klinik; ötiroidi, hipotiroidi, subklinik hipotiroidi ve hipertirodizm gibi geniş bir yelpazeyi kapsar (1, 2).

HT'li hastalar genellikle asemptomatiktir. Guatr görülebilir veya büyüme geriliği gibi nedenlerden dolayı rutin klinik araştırmalar sırasında tesadüfen teşhis edilebilir. Ayrıca otoimmün bozukluğu olan veya kromozomal anormalliklere sahip çocukların düzenli takipleri sırasında da saptanabilir. Teşhis anında hastaların %52,1'inde ötiroidi, %22' sinde hipotiroidi, %19,2'sinde subklinik hipotiroidi ve %6,5'inde ise hipertiroidizm mevcuttur (3).

Hipertiroidizmin en sık nedeni olan GH ise pediatrik yaş aralığında yaygın değildir. Prevalansı 1/10.000 1/100.000 arasında değişmektedir. HT'ye benzer şekilde GH'de kadınlarda erkeklerden 4–5 kat daha fazla görülür. Genellikle 4 yaş üstünde tanı konulur ve ergenlik döneminde zirve yapar. Pediyatrik GH'de büyüme ve kemik olgunlaşmasının hızlanması, okul performanslarında azalma ve davranış değişiklikleri görülebilir (4).

OTH tiroid dışı otoimmün hastalıklar ve genetik bazı hastalıklarda daha sık görülmektedir. Turner sendromu (TS), Down sendromu (DS) ve 22q11.2 delesyon sendromu (22q11.2 DS) gibi genetik anormallikleri olan hastalarda OTH gelişimi normal popülasyona göre daha fazladır. Prader-Willi veya Williams gibi otoimmüniteye bağlı olmayan tiroid disfonksiyonu görülen sendromlar da vardır. Ayrıca Noonan sendromu (NS) ve Nörofibromatozis 1 (NF1) gibi rasopatilerde otoimmün hastalıkların sık görülebileceği bildirilmiştir (5, 6).

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KAYNAKLAR

1. Brown RS. Autoimmune thyroiditis in childhood. Journal of clinical research in pediatric endocrinology. 2013;5 Suppl 1(Suppl 1):45-9.
2. Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. Journal of thyroid research. 2010;2011:675703.
3. Wasniewska M, Corrias A, Salerno M, Mussa A, Capalbo D, Messina MF, et al. Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. Hormone research in paediatrics. 2012;78(4):232-6.
4. Léger J, Kaguelidou F, Alberti C, Carel JC. Graves' disease in children. Best practice & research Clinical endocrinology & metabolism. 2014;28(2):233-43.
5. Kyritsi EM, Kanaka-Gantenbein C. Autoimmune Thyroid Disease in Specific Genetic Syndromes in Childhood and Adolescence. Frontiers in endocrinology. 2020;11:543.
6. Casto C, Pepe G, Li Pomi A, Corica D, Aversa T, Wasniewska M. Hashimoto's Thyroiditis and Graves' Disease in Genetic Syndromes in Pediatric Age. Genes. 2021;12(2).
7. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. The Journal of clinical endocrinology and metabolism. 2006;91(10):3897-902.
8. Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. The Journal of clinical endocrinology and metabolism. 2007;92(1):10-25.
9. Sagi L, Zuckerman-Levin N, Gawlik A, Ghizzoni L, Buyukgebiz A, Rakover Y, et al. Clinical significance of the parental origin of the X chromosome in turner syndrome. The Journal of clinical endocrinology and metabolism. 2007;92(3):846-52.
10. Larizza D, Martinetti M, Lorini R, Dugoujon JM, Tinelli C, Vitali L, et al. Parental segregation of autoimmunity in patients with Turner's syndrome: preferential paternal transmission? Journal of autoimmunity. 1999;12(1):65-72.
11. Chiovato L, Larizza D, Bendinelli G, Tonacchera M, Marinó M, Mammoli C, et al. Autoimmune hypothyroidism and hyperthyroidism in patients with Turner's syndrome. European journal of endocrinology. 1996;134(5):568-75.
12. Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, et al. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. Clinical endocrinology. 2012;76(3):394-8.
13. Grossi A, Crinò A, Luciano R, Lombardo A, Cappa M, Fierabracci A. Endocrine autoimmunity in Turner syndrome. Italian journal of pediatrics. 2013;39:79.
14. El-Mansoury M, Bryman I, Berntorp K, Hanson C, Wilhelmsen L, Landin-Wilhelmsen K. Hypothyroidism is common in turner syndrome: results of a five-year follow-up. The Journal of clinical endocrinology and metabolism. 2005;90(4):2131-5.
15. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. European journal of endocrinology. 2017;177(3):G1-g70.
16. Gawlik A, Gawlik T, Januszek-Trzciakowska A, Patel H, Malecka-Tendera E. Incidence and dynamics of thyroid dysfunction and thyroid autoimmunity in girls with Turner's syndrome: a long-term follow-up study. Hormone research in paediatrics. 2011;76(5):314-20.
17. Valenzise M, Aversa T, Corrias A, Mazzanti L, Cappa M, Ubertini G, et al. Epidemiology, presentation and long-term evolution of Graves' disease in children, adolescents and young adults with Turner syndrome. Hormone research in paediatrics. 2014;81(4):245-50.
18. Aversa T, Gallizzi R, Salzano G, Zirilli G, De Luca F, Valenzise M. Atypical phenotypic aspects of autoimmune thyroid disorders in young patients with Turner syndrome. Italian journal of pediatrics. 2018;44(1):12.
19. Amr NH. Thyroid Disorders in Subjects with Down Syndrome: An Update. Acta bio-medica : Atenei Parmensis. 2018;89(1):132-9.
20. Guaraldi F, Rossetto Giaccherino R, Lanfranco F, Motta G, Gori D, Arvat E, et al. Endocrine Autoimmunity in Down's Syndrome. Frontiers of hormone research. 2017;48:133-46.
21. AlAaraj N, Soliman AT, Itani M, Khalil A, De Sanctis V. Prevalence of thyroid dysfunctions in infants and children with Down Syndrome (DS) and the effect of thyroxine treatment on linear growth and weight gain in treated subjects versus DS subjects with normal thyroid function: a controlled study. Acta bio-medica : Atenei Parmensis. 2019;90(8-s):36-42.

22. Luton D, Azria E, Polak M, Carré A, Vuillard E, Delezoide AL, et al. Thyroid function in fetuses with down syndrome. Hormone research in paediatrics. 2012;78(2):88-93.
23. Pierce MJ, LaFranchi SH, Pinter JD. Characterization of Thyroid Abnormalities in a Large Cohort of Children with Down Syndrome Hormone research in paediatrics. 2017;87(3):170-8.
24. Marchal JP, Maurice-Stam H, Ikelaar NA, Klouwer FC, Verhorstert KW, Witteveen ME, et al. Effects of early thyroxine treatment on development and growth at age 10.7 years: follow-up of a randomized placebo-controlled trial in children with Down's syndrome. The Journal of clinical endocrinology and metabolism. 2014;99(12):E2722-9.
25. van Trotsenburg AS, Vulsma T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, et al. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. The Journal of clinical endocrinology and metabolism. 2005;90(6):3304-11.
26. Claret C, Goday A, Benaiges D, Chillarón JJ, Flores JA, Hernandez E, et al. Subclinical hypothyroidism in the first years of life in patients with Down syndrome. Pediatric research. 2013;73(5):674-8.
27. Meyerovitch J, Antebi F, Greenberg-Dotan S, Bar-Tal O, Hochberg Z. Hyperthyrotropinaemia in untreated subjects with Down's syndrome aged 6 months to 64 years: a comparative analysis. Archives of disease in childhood. 2012;97(7):595-8.
28. Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. The Journal of clinical endocrinology and metabolism. 2014;99(2):363-84.
29. Dos Santos TJ, Martos-Moreno G, Muñoz-Calvo MT, Pozo J, Rodríguez-Artalejo F, Argente J. Clinical management of childhood hyperthyroidism with and without Down syndrome: a longitudinal study at a single center. Journal of pediatric endocrinology & metabolism : JPEM. 2018;31(7):743-50.
30. Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM, Cano-Pérez JF. Hyperthyroidism in a population with Down syndrome (DS). Clinical endocrinology. 2009;71(1):110-4.
31. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. The Journal of clinical endocrinology and metabolism. 2003;88(2):622-6.
32. Bearelly P, Oates R. Recent advances in managing and understanding Klinefelter syndrome. F1000Research. 2019;8.
33. Bojesen A, Juul S, Birkebaek NH, Gravholt CH. Morbidity in Klinefelter syndrome: a Danish register study based on hospital discharge diagnoses. The Journal of clinical endocrinology and metabolism. 2006;91(4):1254-60.
34. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A. Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. Journal of endocrinological investigation. 2017;40(2):123-34.
35. Panimolle F, Tiberti C, Granato S, Anzuini A, Pozza C, Lenzi A, et al. Evidence of increased humoral endocrine organ-specific autoimmunity in severe and classic X-chromosome aneuploidies in comparison with 46,XY control subjects. Autoimmunity. 2018;51(4):175-82.
36. Belling K, Russo F, Jensen AB, Dalgaard MD, Westergaard D, Rajpert-De Meyts E, et al. Klinefelter syndrome comorbidities linked to increased X chromosome gene dosage and altered protein interactome activity. Human molecular genetics. 2017;26(7):1219-29.
37. Bassett AS, McDonald-McGinn DM, Devriendt K, Digilio MC, Goldenberg P, Habel A, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. The Journal of pediatrics. 2011;159(2):332-9.e1.
38. Brunet A, Gabau E, Perich RM, Valdesoiro L, Brun C, Caballín MR, et al. Microdeletion and microduplication 22q11.2 screening in 295 patients with clinical features of DiGeorge/Velocardiofacial syndrome. American journal of medical genetics Part A. 2006;140(22):2426-32.
39. Mahé P, Nagot N, Portales P, Lozano C, Vincent T, Sarda P, et al. Risk factors of clinical dysimmune manifestations in a cohort of 86 children with 22q11.2 deletion syndrome: A retrospective study in France. American journal of medical genetics Part A. 2019;179(11):2207-13.
40. Choi JH, Shin YL, Kim GH, Seo EJ, Kim Y, Park IS, et al. Endocrine manifestations of chromosome 22q11.2 microdeletion syndrome. Hormone research. 2005;63(6):294-9.
41. Shugar AL, Shapiro JM, Cytrynbaum C, Hedges S, Weksberg R, Fishman L. An increased prevalence of thyroid disease in children with 22q11.2

deletion syndrome. American journal of medical genetics Part A. 2015;167(7):1560-4.
42. Bassett AS, Chow EW, Husted J, Weksberg R, Caluseriu O, Webb GD, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. American journal of medical genetics Part A. 2005;138(4):307-13.
43. Brown JJ, Datta V, Browning MJ, Swift PG. Graves' disease in DiGeorge syndrome: patient report with a review of endocrine autoimmunity associated with 22q11.2 deletion. Journal of pediatric endocrinology & metabolism : JPEM. 2004;17(11):1575-9.
44. de Almeida JR, James AL, Papsin BC, Weksburg R, Clark H, Blaser S. Thyroid gland and carotid artery anomalies in 22q11.2 deletion syndromes. The Laryngoscope. 2009;119(8):1495-500.
45. Stagi S, Lapi E, Gambineri E, Salti R, Genuardi M, Colarusso G, et al. Thyroid function and morphology in subjects with microdeletion of chromosome 22q11 (del(22)(q11)). Clinical endocrinology. 2010;72(6):839-44.
46. Cody JD, Ghidoni PD, DuPont BR, Hale DE, Hilsenbeck SG, Stratton RF, et al. Congenital anomalies and anthropometry of 42 individuals with deletions of chromosome 18q. American journal of medical genetics. 1999;85(5):455-62.
47. Tutunculer F, Darendeliler F, Gunoz H, Karaman B, Kayserili H. 18q deletion syndrome associated with autoimmune thyroid disease presenting as hyperthyroidism. Journal of pediatric endocrinology & metabolism : JPEM. 2005;18(4):419-20.
48. Lomenick JP, Smith WJ, Rose SR. Autoimmune thyroiditis in 18q deletion syndrome. The Journal of pediatrics. 2005;147(4):541-3.
49. Dayal D, Giri D, Senniappan S. A rare association of central hypothyroidism and adrenal insufficiency in a boy with Williams-Beuren syndrome. Annals of pediatric endocrinology & metabolism. 2017;22(1):65-7.
50. Levy-Shraga Y, Gothelf D, Pinchevski-Kadir S, Katz U, Modan-Moses D. Endocrine manifestations in children with Williams-Beuren syndrome. Acta paediatrica (Oslo, Norway : 1992). 2018;107(4):678-84.
51. Morris CA, Braddock SR. Health Care Supervision for Children With Williams Syndrome. Pediatrics. 2020;145(2).
52. Chen WJ, Ji C, Yao D, Zhao ZY. Thyroid evaluation of children and adolescents with Williams syndrome in Zhejiang Province. Journal of pediatric endocrinology & metabolism : JPEM. 2017;30(12):1271-6.
53. Selicorni A, Fratoni A, Pavesi MA, Bottigelli M, Arnaboldi E, Milani D. Thyroid anomalies in Williams syndrome: investigation of 95 patients. American journal of medical genetics Part A. 2006;140(10):1098-101.
54. Driscoll DJ, Miller JL, Schwartz S, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors. GeneReviews(®). Seattle (WA): University of Washington, Seattle

55. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. Journal of endocrinological investigation. 2015;38(12):1249-63.
56. Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, et al. Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: effect of GH therapy in 14 children. Hormone research. 2000;53(6):279-87.
57. Vaiani E, Herzovich V, Chaler E, Chertkoff L, Rivarola MA, Torrado M, et al. Thyroid axis dysfunction in patients with Prader-Willi syndrome during the first 2 years of life. Clinical endocrinology. 2010;73(4):546-50.
58. Sharkia M, Michaud S, Berthier MT, Giguère Y, Stewart L, Deladoëy J, et al. Thyroid function from birth to adolescence in Prader-Willi syndrome. The Journal of pediatrics. 2013;163(3):800-5.
59. Festen DA, Visser TJ, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Thyroid hormone levels in children with Prader-Willi syndrome before and during growth hormone treatment. Clinical endocrinology. 2007;67(3):449-56.
60. Iughetti L, Vivi G, Balsamo A, Corrias A, Crinò A, Delvecchio M, et al. Thyroid function in patients with Prader-Willi syndrome: an Italian multicenter study of 339 patients. Journal of pediatric endocrinology & metabolism : JPEM. 2019;32(2):159-65.
61. Eiholzer U, Blum WF, Molinari L. Body fat determined by skinfold measurements is elevated despite underweight in infants with Prader-Labhart-Willi syndrome. The Journal of pediatrics. 1999;134(2):222-5.

62. Heksch R, Kamboj M, Anglin K, Obrynba K. Review of Prader-Willi syndrome: the endocrine approach. Translational pediatrics. 2017;6(4):274-85.
63. Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010;126(4):746-59.
64. Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. Hormone research. 2009;71(4):185-93.
65. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet (London, England). 2013;381(9863):333-42.
66. Svensson J, Carlsson A, Ericsson UB, Westphal O, Ivarsson SA. Noonan's syndrome and autoimmune diseases. Journal of pediatric endocrinology & metabolism : JPEM. 2003;16(2):217-8.
67. Allanson JE. Noonan syndrome. American journal of medical genetics Part C, Seminars in medical genetics. 2007;145c(3):274-9.
68. Quaio CR, Carvalho JF, da Silva CA, Bueno C, Brasil AS, Pereira AC, et al. Autoimmune disease and multiple autoantibodies in 42 patients with RASopathies. American journal of medical genetics Part A. 2012;158a(5):1077-82.
69. DYSCERNE. Noonan Syndrome Guideline Development Group. Management of Noonan Syndrome: A Clinical Guideline Version. 2010.
70. Bizzarri C, Bottaro G. Endocrine implications of neurofibromatosis 1 in childhood. Hormone research in paediatrics. 2015;83(4):232-41.
71. Anderson JL, Gutmann DH. Neurofibromatosis type 1. Handbook of clinical neurology. 2015;132:75-86.
72. Nanda A. Autoimmune diseases associated with neurofibromatosis type 1. Pediatric dermatology. 2008;25(3):392-3.
73. Demirbilek H, Kupeli S, Ozbek MN, Saygi S, Yildirim AT. Neurofibromatosis Type 1 and Autoimmune Hyperthyroidism in a 10.5 Years-Old Girl. Cukurova Medıcal Journal. 2013;38(4).
74. Güler S, Yeşil G, Önal H. Endocrinological Evaluations of a Neurofibromatosis Type 1 Cohort: Is it Necessary to Evaluate Autoimmune Thyroiditis in Neurofibromatosis Type 1? Balkan medical journal. 2017;34(6):522-6.
75. Howell SJ, Wilton P, Lindberg A, Shalet SM. Growth hormone and neurofibromatosis. Hormone research. 2000;53 Suppl 1:70-6.
76. Bergqvist C, Servy A, Valeyrie-Allanore L, Ferkal S, Combemale P, Wolkenstein P. Neurofibromatosis 1 French national guidelines based on an extensive literature review since 1966. Orphanet journal of rare diseases. 2020;15(1):37.
77. Cho EK, Kim J, Yang A, Ki CS, Lee JE, Cho SY, et al. Clinical and endocrine characteristics and genetic analysis of Korean children with McCune-Albright syndrome: a retrospective cohort study. Orphanet journal of rare diseases. 2016;11(1):113.
78. Tessaris D, Corrias A, Matarazzo P, De Sanctis L, Wasniewska M, Messina MF, et al. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Hormone research in paediatrics. 2012;78(3):151-7.