





Neurofibromatosis-Noonan Syndrome, A Rare Case Report

Nörofibromatozis-Noonan Sendromu, Nadir bir olgu sunumu

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ÖZET

Nörofibromatozis- Noonan Sendromu, Nörofibromatozis tip 1 ve Noonan Sendromu özelliklerinin birlikte görüldüğü nadir bir hastalıktır. Nörofibromatozis- Noonan Sendromu vakalarının çoğunda NF1 gen mutasyonu tanımlanmaktadır. NF1 ve PTPN11 gen mutasyonlarının birlikteliği çok az vakada gösterilmiş olup, NF1 ya da PTPN11 denova mutasyonlarına dayandırılmaktadır. Literatürde Nörofibromatozis-Noonan Sendromu olgularında, NF1 mutasyonu olmadan, sadece PTPN11 gen mutasyonu olan vaka göremedik. Biz burada PTPN11 geninde mutasyon olan, Nörofibromatozis-Noonan Sendromu klinik özelliklerine sahip 7 yaşında erkek bir vakayı sunduk. PTPN11 geninde 3 adet homozigot missense mutasyon görüldü (g.584G>T, g.794C>T, g.28145G>C). Veritabanında bu mutasyonların hastalığa neden olabileceği, literatürde ise daha önce tespit edilmediği görüldü.

Anahtar Kelimeler: Nörofibromatozis tip 1, Noonan Sendromu, cafe-au-lait lekeleri, kısa boy, çocuk

ABSTRACT

Neurofibromatosis-Noonan syndrome is a rare disorder which shows the features of both neurofibromatosis type 1 and Noonan syndrome. Mutations in the NF1 gene were identified in majority of Neurofibromatosis-Noonan Syndrome cases. The co-occurrence of NF1 and PTPN11 mutations has been shown in very few studies and has been attributed to a denova mutation either in NF1 or PTPN11. We didn't see PTPN11 gene mutations without NF1 mutations in Neurofibromatosis-Noonan Syndrome patients in the literature. Here, we report a 7-year-old boy who had clinical features of Neurofibromatosis-Noonan Syndrome with a mutation in the PTPN11 gene. He has 3 homozygous missense mutation in PTPN11 gene (g.584G>T, g.794C>T, g.28145G>C). These mutations are shown that the cause of disorder at database but it was not found any manuscript in the literature.

Key words: Neurofibromatosis type 1, Noonan Syndrome, café-au-lait macules, short stature, children



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INTRODUCTION

Neurofibromatosis type 1 (NF1) is relatively common with an incidence of 1 in 3000 live births. Despite the pattern of autosomal dominant inheritance, sporadic cases also may occur. Due to mutations in the NF1 gene, located at chromosome 17q11.2, loss of function becomes in the neurofibromin, leading to the NF1 phenotype (clinical and molecular) (1). Common characteristics include café-au-lait macules, neurofibroma, optic glioma, Lisch nodule and the other system findings.

Noonan syndrome (NS) is an autosomal dominant disorder which is characterised by dysmorphic face (hypertelorism, downslanting palpebral fissures, low set and posteriorly rotated ears, micrognathia), congenital heart defects (pulmonic stenosis), short stature, skeletal anomalies. NS is affecting approximately 1 in 1000– 2500 live births (2). Approximately 50 percent of children with Noonan syndrome have a missense mutation in the Ras signaling pathway, especially PTPN11 gene (protein-tyrosine phosphatase, nonreceptor-type, 11), located as chromosome 12q24 (3).

Neurofibromatosis-Noonan syndrome (NFNS) is a rare disorder which shows the features of both NF1 (neurofibromatosis 1) and Noonan syndrome (NS). Mutations in the NF1 gene were identified in majority of NFNS cases(4). The co-occurrence of NF1 and PTPN11 mutations has been shown in very few studies and has been attributed to a de novo mutation either in NF1 or PTPN11 gene(5). Here, we report a 7-year-old boy who had clinical features of NFNS with a mutation in the PTPN11 gene.

CASE PRESENTATION

The male patient was admitted to our hospital at the age of 7 year old. He was examined because of his dysmorphic face and café-au-lait macules. He wasn't the product of a consanguineous marriage. He was born via normal vaginal delivery at 38 weeks. He did not have any systemic disorder. Dysmorphic facial features included frontal bossing, high forehead, hypertelorism, epicanthal fold. The patient had 14 café-au-lait macules (>5 mm) and axillary freckling. The biggest spot (4 cm) was on the patient's back. His weight was 21 kg (-1,44 SD), his height was 115,5 cm (-2,17 SD). Growth velocity was < 4 cm/year (< -2 SD). The weight according to height was 102. Bone age was 5 year. Target height was 158,5 cm. The patient's pubertal stage was evaluated as Tanner stage 1. The patient did not have any neurofibroma. The nervous system and cardiovascular examination was completely normal. There was hypermetropia and astigmatism in the ocular examination. There was not Lisch nodules and optic glioma.

Considering short stature and the other signs together, genetic analyses were performed for the patient to investigate

NFNS and the genetic analysis revealed 3 mutation in the PTPN11 gene. No mutation was found in NF1 gene with Fish (Fluorescence in situ hybridization) and MLPA (Multiplex Ligation-dependent Probe Amplification) analysis.

DISCUSSION

NF-Noonan syndrome (NFNS) (OMIM 601321) is a hybrid syndrome, combining manifestations of neurofibromatosis type 1 and Noonan syndromes, which are separate syndromes (6,7,8). Determining the molecular basis of NFNS has advanced since the identification of NF1 and PTPN11 mutations for NF1 and NS, respectively. NFNS results from diverse mutations at distinct genes. These genes are affecting a common intracellular signal transduction pathway called RAS-MAPK (mitogen-activated protein kinase) pathway. This pathway plays roles in apoptosis, cell proliferation and differentiation. The localization of affected gene in the RAS-MAPK pathway and diversity of the mutations in these genes cause various different phenotypic characteristics and different syndromes. Since these syndromes are associated with the effects on the same pathway, they are called 'RASopathies' or RAS-MAPK syndromes. NFNS is an important RASopathy. Colley et al. and Bahuau et al. documented independent segregation of NF1 and NS traits in two families (9,10). The co-occurrence of NF1 and PTPN11 mutations has been shown in very few studies and has been attributed to a de novo mutation either in NF1 or PTPN11. Bertola et al. reported a patient with NF1 and NS features who carried a heterozygous mutation in both NF1 and PTPN11 (5). Carey et al. and Stevenson et al. reported co-segregation of NS with mild NF1 features with a NF1 mutation (11,12). Baralle et al. revealed NF1 mutations in two of six NFNS patients (13). De Luca et al. demonstrated NF1 mutations in 16 of 17 NFNS patients and excluded PTPN11 mutations in all of them (14). Hüffmeier et al. reported all patients who carried a heterozygous mutation or a heterozygous deletion of one NF1 copy (15). Our patient has 3 homozygous missense mutation in PTPN11 gene (g.584G>T, g.794C>T, g.28145G>C) These mutations are shown that the cause of disorder at database but it was not found any manuscript in the literature. We didn't see PTPN11 gene mutations without NF1 mutations in NFNS patients in the literature. Our patient's parents did not give permission, therefore we could not send genetic analysis from his mother and father. If we study genetic analysis from his parents, the mutations can be clarified in our minds.

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