

Right amelia in a patient with neurofibromatosis type 1

Nörofibromatozis tip 1'li hastada sağ amelia

Hilal Aydın¹

¹ Department of Pediatric Neurology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey

ORCID ID of the author(s)

HA: 0000-0002-2448-1270

Abstract

Neurofibromatosis type 1 (NF1) affects many different systems such as the skeletal, endocrine, gastrointestinal systems, as well as the skin, peripheral and central nervous systems (CNS). The NF-1 gene, located in the 11p12 region of chromosome 17, encodes a tumor suppressor protein, called neurofibromin, and is expressed in a diverse range of cell and tissue types. Neurofibromin negatively regulates the activity of an intracellular signaling molecule, p21ras (Ras), acting as a GTPase-activating protein (Ras-GAP). The Ras-GAP function of neurofibromin has been associated with various NF1-related clinical symptoms. We aimed to present a case of clinically and genetically diagnosed neurofibromatosis type 1 with a developmental anomaly in the right hand (right hand amelia). Our knowledge about whether the coexistence of these two conditions is coincidental or a result of neurofibromatosis is limited. We wanted to present this case since the coexistence of amelia and neurofibromatosis is a first.

Keywords: Neurofibromatosis type 1, Amelia, Neurofibromin

Öz

Nörofibromatozis tip 1 (NF1); deri, periferik ve santral sinir sistemi (SSS) yanında kemik, endokrin, gastrointestinal sistem gibi bir çok değişik sistemi etkiler. Otozomal dominant geçişli olup görülme sıklığı 1/3000-1/4000 olarak saptanmıştır. NF-1 geni 17. kromozom 11p12 bölgesindedir, bu gen nörofibromin olarak adlandırılan tümör supresör bir proteini kodlamaktadır. NF1 geni, nörofibromin proteini kodlar, çok çeşitli hücre ve doku tiplerinde ekspres edilir. Nörofibromin, bir GTPaz aktive edici protein (Ras-GAP) olarak işlev göerek hücre içi bir sinyal molekülü p21ras'ın (Ras) aktivitesini negatif olarak düzenler. Nörofibrominin Ras-GAP fonksiyonu, NF1 ile ilişkili çeşitli klinik semptomlarla ilişkilendirilmiştir. Bu yazıda Nörofibromatozis tip 1 klinik ve genetik olarak tanısı konulan ve sağ elde gelişimsel anomalisi (sağ el amelia) olan bir vakayı sunmayı hedefledik. Bu iki durum birlikteliğinin koinsidental mi olduğu yada nörofibromatozis sonucu mu olduğu konusunda bilgilerimiz yetersiz kalmaktadır. Amelia ve nörofibromatozis birlikteliği bir ilk olduğu için bu vakayı sunmak istedik.

Anahtar kelimeler: Nörofibromatozis tip 1, Amelia, Nörofibromin

Introduction

Neurofibromatosis type 1 (NF1) affects many different systems such as the skeletal, endocrine, gastrointestinal systems, as well as the skin, peripheral and central nervous systems (CNS). It is an autosomal dominant disease with an incidence of 1 in 3000-4000 individuals [1]. The NF-1 gene, located in the 11p12 region of chromosome 17, encodes a tumor suppressor protein, called neurofibromin, and is expressed in a diverse range of cell and tissue types [2]. The diagnosis of NF1 is made based on the coexistence of at least two of the diagnostic criteria defined by the National Institute of Health (NIH): 1-6 or more café au lait macules of 5 mm in prepubertal individuals and >15 mm in post-pubertal individuals, 2- Freckling in the axillary or inguinal regions, 3- Two or more neurofibromas or one plexiform neurofibroma, 4- Optic glioma, 5- Osseous lesion, 6- At least two iris hamartomas (Lisch nodule), 7- A first-degree relative diagnosed with NF1 [1]. In this article, we aimed to present a case of clinically and genetically diagnosed Neurofibromatosis type 1 with a developmental anomaly in the right hand (right hand amelia).

Corresponding author / Sorumlu yazar:
Hilal Aydın

Address / Adres: Balıkesir Üniversitesi Tıp Fakültesi, Çocuk Nörolojisi Anabilim Dalı, Çayırhisar, 10145, Balıkesir, Türkiye
e-Mail: drhilalaydin@gmail.com

Informed Consent: The authors stated that the written consent was obtained from the parents' of the patient presented with images in the study.

Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 2/29/2020
Yayın Tarihi: 29.02.2020

Copyright © 2020 The Author(s)
Published by JOSAM

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and build upon the work provided it is properly cited. The work cannot be used commercially without permission from the journal.



Case presentation

A 7.5-year-old girl presented with café au lait macules on her body. The patient's prenatal and natal history were insignificant, her neuromotor development was normal and she underwent surgery for pseudoarthrosis of the left tibia at the age of 4 years. There was no history of consanguinity. It was stated that the mother of the patient was diagnosed with neurofibromatosis type 1 and did not go to control visits regularly. When the history of the patient was detailed, it was learned that genetic analysis was ordered with the pre-diagnosis of neurofibromatosis, but the result was not pursued by the family. On her physical examination, her general condition was good, vital signs were stable, head circumference was 52 cm (0, +2SD), she was cooperative, orientated, and other systemic examinations were normal except for multiple café au lait macules on the body, developmental anomaly in the right hand (right hand amelia), and kyphoscoliosis (Figure 1). The abdominal ultrasonography, echocardiography, fundus, and hearing tests of the patient were performed, and all were found normal. The laboratory tests including hemogram, transaminases, renal function tests, the electrolytes, 25-OH vitamin D, thyroid function test, folate, and vitamin B12 levels were normal. The cranial imaging revealed T2A and FLAIR hyperintensity in bilateral basal ganglia. She was referred to orthopedics because of kyphoscoliosis. No additional pathology was identified in the follow-ups of the patient who was closely monitored.



Figure 1: Developmental anomaly in the right hand (right hand amelia) of Neurofibromatosis Type 1 patient

Discussion

The incidence of congenital anomalies is expected to be high in NF1. The common congenital anomalies include spina bifida, fusion of vertebral bodies, congenital hip dislocation, club-foot deformities and spondylolysis [3]. Although congenital skeletal anomalies are not characteristic of neurofibromatosis, they probably represent one aspect of the disease in which mesodermal dysplasia is manifested. Osseous abnormalities are present in 40% of patients with NF1. The most common skeletal deformity is kyphoscoliosis [4]. Although about 50% of cases

with congenital pseudoarthrosis are due to NF, only 0.5 to 1% of NF patients have pseudoarthrosis. Congenital pseudoarthrosis most commonly occurs in the tibia [5].

The NF1 gene encodes the neurofibromin protein and is expressed in a diverse range of cell and tissue types. Neurofibromin negatively regulates the activity of an intracellular signaling molecule, p21ras (Ras), acting as a GTPase-activating protein (Ras-GAP). The Ras-GAP function of neurofibromin has been associated with various NF1-related clinical symptoms [6]. The difficulties in understanding the human pathophysiology of skeletal defects in NF1 have led to the development of mouse models to determine the role of NF1 in bone cells and to facilitate preclinical studies. NF1 mRNA and neurofibromin are expressed during puberty and development in mouse bone and cartilage, and more specifically in mesenchymal stem cells, corneocytes, osteoblasts and osteoclasts. This expression pattern has shown that NF1-related skeletal defects are caused by primary bone defects resulting in bone cellular dysfunction and/or partially generalized NF1 heterozygosity due to loss of NF1 function in specific bone cells [7]. The Ras/MAPK pathway interacts with the FGF signaling pathway, including targets such as SHH (sonic hedgehog), a crucial factor in bone formation and limb development. In the literature, the association of polydactyly and NF was investigated, and Kimes et al. stated that neurofibromin deficiency disrupts Ras / MAPK pathway, affects downstream SHH targets and ultimately causes extra finger formation. In the literature, there are publications indicating whether the association of NF1 and polydactyly is coincidental or related to pathogenesis [8].

Congenital anomalies affect approximately 1-2% of newborns. About 10% of these malformations involve the upper extremities. The congenital transverse deficiency is defined according to the last remaining bone segment from aplasia to amelia. These defects are partial or complete absence due to disruption of apical ectodermal ridge, its signaling or vascular abnormalities. Amelia is a birth defect characterized by the absence of one or more limbs. It is a rare condition with an incidence ranging from 0.053 to 0.095 in 10,000 live births. Although it is usually sporadic, it is less frequently involved in autosomal recessive/dominant or sex-linked inheritance. Amelia can be identified as an isolated defect, but it can often coexist with major malformations of other organ systems [9], including cleft lip and/or palate, body wall defects, head shape anomalies, kidney, diaphragm and spinal canal defects. It may coexist with facial clefts and facial anomalies. Diaphragm may or may not be herniated and one or both kidneys may be small or absent. Infants with only amelia have a good prognosis, while patients with organ malformations are lost at the first age due to complications [10]. Although our patient had isolated amelia, all abdominal ultrasonography, echocardiography, eye, and hearing tests performed for concomitant pathologies were normal.

Conclusions

Considering the literature, it is seen that patients with neurofibromatosis type 1 have a variety of skeletal deformities. However, the coexistence of amelia and neurofibromatosis has not been found in the literature. The Ras/MAPK pathway interacts with the FGF signaling pathway, including targets such as SHH (sonic hedgehog), a crucial factor in bone formation,

limb development. Neurofibromin deficiency also causes disruption of the RAS/MAPK pathway. Our knowledge about whether the coexistence of these two conditions is coincidental or a result of neurofibromatosis is limited. Further molecular and functional genetic studies are needed in this aspect.

References

1. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45:575-8.
2. Viskochil D. Genetics of neurofibromatosis 1 and the NF1 gene. J Child Neurol. 2002;17:562-70.
3. Eleftheriou F, Kolanczyk M, Schindeler A, Viskochil DH, Hock JM, Schorry EK. Skeletal abnormalities in neurofibromatosis type 1: approaches to therapeutic options. Am J Med Genet. 2009;149a:2327-38.
4. Georgescu EF, Stanescu L, Georgescu AC, Dumitrescu D, Foarfa C, Calin G. Bone abnormalities occurring in the follow-up of the patients with neurofibromatosis type 1. Romanian Journal of Morphology and Embryology. 2007;48(3):249-56.
5. Kristiansen LP, Steen H, Terjesen T. Residual challenges after healing of congenital pseudarthrosis in the tibia. Clin Orthop. 2003;414:228-37.
6. Schindeler A, Little DG. Recent insights into bone development, homeostasis, and repair in type 1 neurofibromatosis (NF1). Bone. 2008;42:616-22.
7. Yang FC, Chen S, Robling AG, Yu X, Nebesio TD, Yan J, et al. Hyperactivation of p21 and PI3K cooperate to alter murine and human neurofibromatosis type 1-haploinsufficient osteoclast functions. J Clin Invest. 2006;116:2880-91.
8. Kimes KL, Han MJ, Brown PJ. Polydactyly in neurofibromatosis type I: a potential clue to diagnosis. Dermatol Online J. 2016;22(11):7-11.
9. Chaudhary R, Singh K. A Rare Fetal Congenital Anomaly: Meromelia. Journal of Gynecology. 2018;1(13):1-5.
10. Yesender M, Anjum A, Saritha S, Rao SB, Ramani TV, Ericson P. Limb defects: a spectrum of correlated study. International Journal of Anatomy and Research. 2016;4(1):1810-8.

This paper has been checked for language accuracy by JOSAM editors.

The National Library of Medicine (NLM) citation style guide has been used in this paper.