Rare presentation of neurofibromatosis and Turner syndrome in a pediatric patient

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Abstract

Neurofibromatosis type 1 (NF1) is classically defined by the presence of multiple *café-au-lait* macules as one of the diagnostic criteria. Turner syndrome (TS) can also present with *café-au-lait* macules along with short stature. Our patient is the fifth reported with both NF1 and TS and the first who has been on growth hormone for short stature associated with TS.

Introduction

Solitary *café-au-lait* macules are common birthmarks,[1] which can vary in color from light to dark brown, with borders that can be smooth or irregular. When multiple *café-au-lait* macules are present, neurofibromatosis type 1 (NF1) should be considered. NF1 is an autosomal dominant disorder due to loss-of-function mutations in the tumor suppressor *NF1* gene (*neurofibromin 1*).[2] The worldwide incidence of NF1 is estimated to be 1 in 2500 to 3000 individuals.[3,4] It is a clinical diagnosis based on the presence of at least 2 of 7 diagnostic criteria.[5] One of the 7 criteria include 6 or more *café-au-lait* macules ≥5 mm in diameter in pre pubertal, and ≥15 mm in post pubertal children.[5]

Turner syndrome (TS) can also present with *café-au-lait* macules.[6] TS occurs due to loss of either all or part of the X chromosome, with an incidence of at least 1 in 2500 live births.[7]

Four patients with overlapping phenotypic features of both NF1 and TS have been previously reported.[8-10] We report the fifth girl diagnosed with NF1 and TS who presented with *café-au-lait* macules.

Case Report

An 8-year-old female presented to our clinic for continued evaluation of short stature due to TS. She had been diagnosed with TS when chromosome analysis at age 6 for short stature revealed 45X karyotype (Universidad Autónoma de Santo Domingo, Dominican Republic). She was started on growth hormone (GH) therapy to promote linear growth. Initially 3 *café-au-lait* macules were reported on clinical examination. At age 8 years, a clinical diagnosis of NF1 was made based on presence of more than 6 *café-au-lait* macules measuring >5 mm in diameter, axillary freckling, and Lisch nodules on ophthalmologic examination. A novel heterozygous p.M1149V variant of uncertain significance was identified by genetic testing (Center for Human Genetics, Inc., Cambridge, MA, USA). It was predicted that this variant would not be tolerated based on SIFT (http://sift.jvci.org), and probably damaging using Polymorphism Phenotyping v2 (PolyPhen2) (http://genetics.bwh. Harvard.edu/pph2). As the amino acid was conserved amongst species, and p.M1149I variant had been reported as disease causing, it was concluded that p.M1149V variant was likely pathogenic.

Discussion

NF1 is a RASopathy, a class of developmental disorders caused by germline mutations in genes that regulate the Ras/mitogen-activated protein kinase (MAPK) pathway.[11] RASopathies produce a group of phenotypically overlapping syndromes, which, in addition to NF1, include Noonan syndrome (NS) and Noonan-like syndrome.[11] Another RASopathy called Neurofibromatosis-Noonan syndrome (NFNS), first recognized in 1985 by Allanson *et al.*[12] shows phenotypic overlap between NF1 and NS. Although NS and TS share phenotypic similarities, which resulted in patients with NS previously diagnosed with a form of TS, they are distinct genetic conditions. Our patient is the fifth reported with clinical features of both NF1 and TS. Interestingly, the same pathogenic variant, p.M1149V, that was identified in *NF-1* in our patient has been reported in another patient with NF1,[13] who was also diagnosed with mitochondrial complex I deficiency based on investigation for progressive microcephaly. This again was presumed to be coincidental. Our patient was prescribed GH therapy for the FDA approved indication of short stature due to TS.[14] Short stature, and GH deficiency (GHD) have also been reported as more common in children with NF1 than the general population.[15] The exact incidence and cause of GHD have not been clearly defined. However, as NF1 has an increased risk for development of benign and malignant tumors, there has been a long-standing concern about the safety of GH therapy in NF1 patients. Review of data from 102 NF1 children on GH therapy[16] showed the incidence of intracranial tumor occurrence was comparable to that in NF1 patients not treated with GH.[17-19] Interestingly, in NF1 patients, GH receptor (GHR) expression was identified in plexiform neurofibromas,[20] which are common precursors of malignant peripheral nerve sheath tumors in NF1.[21] Although this does not prove a role of GH in development of these neurofibromas and a link to malignant transformation, the presence of GHR suggests that these tumors may respond to GH.

Conclusions

Although the 2 distinct genetic syndromes in our patient are presumably a chance occurrence, it remains important for clinicians to recognize that the presence of one genetic condition that can explain a specific clinical presentation, does not exclude a second. We plan to monitor our patient closely both clinically and biochemically due to the potential risk of malignant transformation of her fibromas on GH therapy.

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