Neurofibromatosis Type 1 Associated with Dysplastic Nevus Syndrome

Zrinka Paštar¹, Jasna Lipozenčić¹, Suzana Kovačević², Samir Ćanović², Ana Didović-Torbarina², Anamarija Vukasović³

¹University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb; ²Department of Ophthalmology, Zadar General Hospital, Zadar; ³University Department of Nuclear Medicine, Dubrava University Hospital, Zagreb, Croatia

Corresponding author:
Professor Jasna Lipozenčić, MD, PhD
University Department of Dermatology and Venereology
Zagreb University Hospital Center and School of Medicine
Šalata 4
HR-10000 Zagreb
Croatia
jasna.lipozencic@zg.htnet.hr

Received: October 22, 2008
Accepted: April 17, 2009

SUMMARY Neurofibromatosis type 1 (NF-1) is an autosomal dominant disorder that primarily affects the development and growth of neural cell tissues. It causes tumors to grow on nerves and produces other abnormalities such as skin changes and bone deformities. Dysplastic nevus syndrome (DNS) represents multiple atypical nevi associated with polygenetic inheritance pattern and may rarely occur together with NF-1. DNS type A is a marker of increased melanoma risk, while melanoma has been rarely reported in patients with NF-1. We describe a case of NF-1 type A with DNS presenting with multiple neural tumors, café-au-lait spots, hamartomas in globus pallidus and pigmented melanocytic iris hamartomas (Lisch nodules). The importance of close follow up of nevi in such patients with NF-1 and DNS for the development of melanoma as well as other NF-1 associated skin disorders and with multidisciplinary approach to other associated diseases is highlighted.

KEY WORDS: neurofibromatosis type 1, dysplastic nevus syndrome, melanoma

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is the most common phakomatosis, an autosomal dominant disorder with one of the highest mutation rates (1,2). NF-1 by mutation of the tumor suppressor activity gene encoding neurofibromin protein affects primarily the development and growth of neural cell tissues and the regulation of melanogenesis (3). NF-1 is characterized by tumors originating from the neural crest, especially brain tumors and endocrine malignancies, and produces skin changes, vascular and skeletal dysplasias (1,3,4). Dysplastic nevus syndrome (DNS) represents multiple atypical melanocytic nevi associated with polygenetic inheritance pattern. Although rare, it may occur together with NF-1 (4,5). DNS type A is a marker of increased melanoma risk, while melanoma has been rarely reported in NF-1 (2,4-6). We present a case of NF-1 associated with DNS type A.
CASE REPORT

A 17-year-old boy was referred to our Department for clinical and dermoscopic follow up of DNS. NF-1 was diagnosed at the age of four when the patient began developing café au lait maculae, and appendicitis and a volvus of ileum because of ganglioneuromatosis of the gastrointestinal tract. At the age of 15, axillary and inguinal freckles, and numerous subcutaneous nodular neurofibromas started to appear.

Physical examination revealed greenish skin discoloration, numerous café au lait maculae, axillary and inguinal freckles, numerous subcutaneous nodular neurofibromas on the trunk and extremities, and more than 50 dysplastic nevi (Fig. 1A-C), mainly a combination of reticular, globular and unspecific global pattern on dermoscopy.

Additionally, scoliosis, discrete trunk asymmetry and incomplete painful extension of the knees were present. Periodically he had radicular pain in his legs and right shoulder. On the last check-up, additional findings were observed: slit-lamp examination showed multiple pigmented iris hamartomas (Lisch nodules); nuclear magnetic resonance (NMR) showed multiple neurofibromas in subcutaneous and paratracheal muscle region; all along the spinal cord but mainly in the left nuchal region and lumbosacral region bilaterally, within the spinal canal, intervertebral foramina and paraspinally, and also in the retroperitoneal and pelvic region NMR showed multiple neurofibromas that were in concordance with pain; NMR revealed hamartoma in the area of globus pallidus on the left side of crura cerebri; x-ray of distal metaphysis of the right lower leg showed an ovoid transparent zone.

Family history for NF-1 was positive as the father had the disease. The linkage analysis using polymorphic gene markers of NF-1 (exon 5 RsaI polymorphism) revealed the pHHR202/Rsal haplotype that is inherited through generations (Fig. 2). As there was no family history of DNS and melanoma, the diagnosis of DNS type A (sporadic DNS without melanoma) was established (7,8).

DISCUSSION

The knowledge of the migration, differentiation and physiologic phenotypes of the tissues of the neural crest is essential for understanding the pathogenesis of NF-1. Neurocristopathy is a term that unites a variety of dysgenetic, hamartomatous and neoplastic conditions originating in the neural crest (9). These tumors are peripheral sheath tumors, mostly malignant schwannoma, astrocytoma, glioblastoma but also endocrine malignancies such as pheochromocytoma and thyroid medullary carcinoma (3,4). Malignant transformation of the nerve sheath tumors is characterized by acceleration in growth and change in configuration, and it has been reported in 2%-40% of patients with NF-1 (9).

The association between congenital melanocytic nevi and NF-1 has been reported in 1%-15% of patients (5,10,11). An increased risk of giant congenital melanocytic nevi has also been reported in patients with NF-1 (5,12,13). Moreover, melanocytic nevi were identified in 11% of patients with NF-1 (5,10). Additionally, neurofibromas in...
patients with NF-1 are reported to be associated with melanocytic nevi but not with sporadic neurofibromas (10). Moreover, reports of melanocytic malignancies such as uveal, leptomeningeal, mucosal, penile, cutaneous melanoma, and melanoma within congenital nevi in association with NF-1, and also cutaneous melanoma in association with both NF and DNS are rare, and an increased risk has not been clearly demonstrated (Table 1) (2-4,9,13-17). According to Guillot et al., an increase in melanoma incidence in patients with NF1 remains hypothetical but a small series of malignant melanoma arising in NF-1 patients displays a large female predominance, higher thickness and frequent association with a second neoplasia (4).

Furthermore, NF-1 patients have an increased number of melanocytes in the café au lait spots as well as in their normal skin, suggesting a proliferative process of melanocytes in NF-1 (2,9). The melanocyte, a neural crest derivative, is not only responsible for one of the most prominent features of NF, café au lait maculae, but also for melanocytic pigmented iris hamartomas, choroidal multifocal and bilateral nevi, uveal nevi in general, cutaneous nevi and congenital giant melanocytic nevi (5,9). Uveal nevi in general, but mainly choroidal nevi may present an increased risk for the development of uveal melanoma, although some studies did not detect such an association (18-20).

The possible mechanism of the occurrence of malignancies with NF-1 is a mutation of the neurofibromin protein that participates in cell prolif-
eration control by inactivation of p21 ras. Furthermore, the neurofibromin protein is a regulator of melanogenesis as an activator of the tyrosinase gene promoter (3,4,13) Moreover, in sporadic melanoma cell lines, mutations in NF-1 gene have been described (3,4). Also, allelic loss of the NF-1 gene locus has been described in desmoplastic neurotropic melanoma (6). However, two cases of melanoma associated with NF in two first degree relatives from a family with DNS have been described (9). Furthermore, multiple congenital melanocytic nevi presenting with neurofibroma-like lesions complicated by melanoma have been reported (15). DNS distinguishes type A, B, C, D-1 and D-2 differentiating between sporadic and familial type and connection to positive melanoma history (7,8). DNS is a marker of the melanoma risk and the risk rises with the type of DNS (8). Hence, in our patient there was NF-1 with a still unknown increased risk of melanoma and DNS type A with a known risk of cutaneous and ocular melanoma, thus presenting a complex problem.

CONCLUSION
A case of NF-1 with DNS type A presenting with multiple neural tumors, café au lait spots, hamartomas in globus pallidus and pigmented iris hamartomas is described. Although NF and cutaneous melanoma are both diseases of neuroectodermal origin, reports of their association are rare and the relation between cutaneous melanoma and NF has not yet been definitely established. Additionally, the effect of NF-1 mutations in melanoma risk patients with both NF-1 and DNS is not known. Although DNS could possibly be seen as the underlying disease, research into pigmented disturbance in NF-1 is necessary to give definitive explanation.

We emphasize the importance of close follow up of nevi in patients with NF-1 and DNS for the development of melanoma as well as other NF-1 associated skin disorders, and the multidisciplinary approach to other associated diseases.

References


How to solve wrinkles - use Tokalon cream; year 1929. (from the collection of Mr. Zlatko Puntijar)