Letter

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Ectropion Uveae in neurofibromatosis type 1: a new manifestation

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Abstract

Neurofibromatosis type 1 (NF1) is a rare genetic disorder with an autosomal dominant transmission and an estimated incidence of 1:2500-3500 live birth. Penetrance is virtually 100%, but the expression is highly variable and almost every organ can be affected. Diagnosis of NF1 is made with at least two of the following diagnostic criteria: six or more cafè-au-lait spots, two neurofibromas or one plexiform neurofibroma, axillary or groin freckling, optic glioma, two Lisch nodules, bone dysplasia and first-degree relative with NF1. Other ocular manifestations include orbital neurofibromas, cafè-au-lait spots on the eyelids, congenital dysplasia of the sphenoids wing and congenital glaucoma and choroidal abnormalities. Congenital Ectropion Uveae (CEU) is a rare, non-progressive anomaly characterized by the presence of iris pigment epithelium on the anterior surface of the iris stroma, resulting from its proliferation. CEU probably depends on embryological disorders in neural cells and/or neuroectoderm of the optic cell. In this paper the authors describe three patients with CEU and NF1 found in 243 consecutive NF1 patients. ***Clin Ter 2021; 172 (3):206-208. doi: 10.7417/CT.2021.2314***

Key words: *Neurofibromatosis type 1, ectropion uveae*

Dear Editor,

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is one of the most common genetic diseases, affecting 1 in 2.500 to 3.500 people worldwide, irrespective of sex or ethnic origin (1-3). NF1 is an autosomal dominant disorder caused by a defect in a single gene with complete penetrance. The NF1 gene, located on chromosome 17q11.2, encodes for neurofibromin, a cytoplasmic protein expressed in many cells that functions as a negative regulator of the Ras protooncogene, a key signaling molecule in the control of cell growth. Most mutations of the NF1 gene produce a truncated form of neurofibromin and disrupt the normal cell cycle regulation (4,5). This may explain why patients with NF1 have a higher risk of benign and malignant tumors (6-10).

The diagnosis is clinical and it is based on the presence of at least two of the following criteria: 6 or more cafè-au-lait spots, 2 or more cutaneous neurofibromas, 1 or more plexiform neurofibromas, axillary or groinal freckling, optic glioma, 2 or more iris Lisch nodules, distinctive bony lesions, and a first-degree relative with NF1 (11).

NF 1 may involve almost every organ system in the body, with considerable inter-familial and intra-familial variation, there may be ophthalmologic, cutaneous, musculoskeletal, cardiovascular, gastrointestinal, autoimmune, endocrine, central and peripheral nervous system, and learning alterations (12-21). The most common ocular feature of NF1 is the Lisch nodules of the iris, which are described as "iris hamartomas". Other ocular manifestations include optic gliomas, orbital neurofibromas, cafè-au-lait spots on the eyelids, congenital dysplasia of the sphenoids wing, congenital glaucoma, choroidal abnormalities and retinal microvascular abnormalities (22-25).

Congenital Ectropion Uveae (CEU) is a rare, non-progressive anomaly characterized by the presence of iris pigment epithelium on the anterior surface of the iris stroma and occasionally associated with other ocular or systemic defect. It results from proliferation of the pigment epithelium on the anterior surface of the iris from the pigment ruff, where the two layers of the retinal pigment epithelium are continuous (26).

In this paper we describe three patients with CEU and NF1 found in 243 consecutive NF1 patients, all followed at the University of Rome 'Sapienza', Umberto I Hospital, Italy and undergoing an ophthalmological examination.

The mean age of the three patients with CEU and NF1 was 25 years-old (8-32-35); two were male and one was female. Family history was recorded in two subject. Diagnosis of NF1 was made according to criteria from the NIH Consensus Conference. All presented café-au-lait spots and freckles; two had neurofibromas (Fig. 1) and one, the younger patient, had scoliosis.

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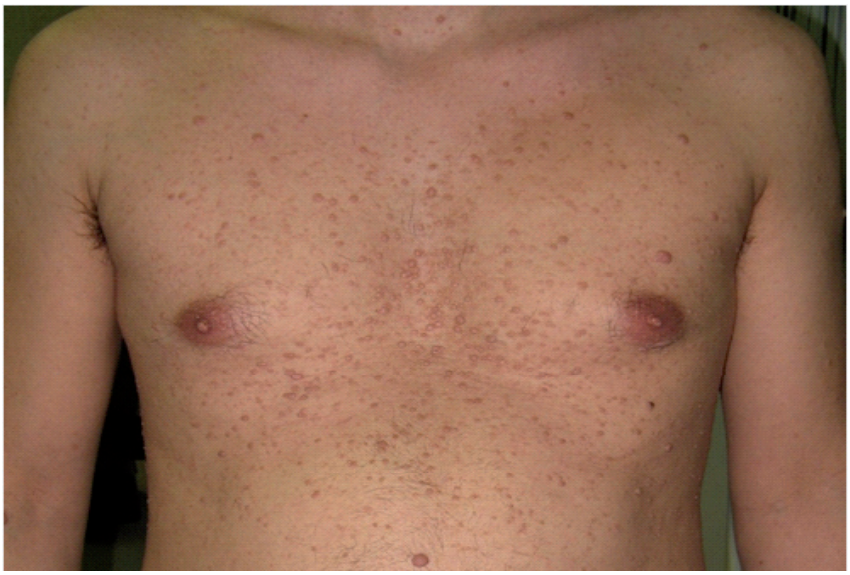

Fig. 1. Multiple neurofibromas of the trunk in a patient with NF1.

Ophthalmological examination revealed best-corrected visual acuity of 55 letters in five eyes (ETDRS system) and 45 letters in one eye (ETDRS system). All our patients presented unilateral CEU, specifically localized in the right eye (Fig. 2) in two patients and in the left eye in one patient. Intraocular pressure measurement was normal in two patients both in the affected and not affected eye (without therapy). The third and youngest patient showed an intraocular pressure at the highest limits (19 mmHg) in the affected eye, despite instillation of beta blockers. The other eye showed a normal pressure without therapy. The anterior segment of the eyes showed Lisch nodules in all patients. The patients had no family history of ectropion uveae or any other ophthalmic disease.

NF1 may involve almost every body structure, with considerable inter-familial and intra-familial variation. It is characterized by the appearance of various cutaneous, ocular and neurological manifestations. The association between NF1 and CEU has been rarely reported. In 1984 Ritch reported 8 patients with unilateral CEU of which 3 had neurofibromatosis (27). In 1991 Burke observed a case of NF1 in association with congenital iris ectropion (28). In 2004 Trovò-Marqui described a patient with ectropion and the mutation R1748X in the NF1 gene (29). In our case we found unilateral CEU in 1.2% of the cases (3/243). Our study is the first that also assessed the true prevalence of CEU in a large population of NF1 patients.

As the most important complication of CEU is congenital or juvenile glaucoma, the NF1 patients should be examined for the presence of ectropion and, consequently, for the development of glaucoma. The pathogenesis of CEU is still uncertain but probably depends on embryological disorders in neural cells and/or neuroectoderm of the optic cell (30). According to this the association between CEU and NF1 could be not a coincidental finding and therefore further studies are needed to understand what are the real pathogenetic mechanisms underlying this association.

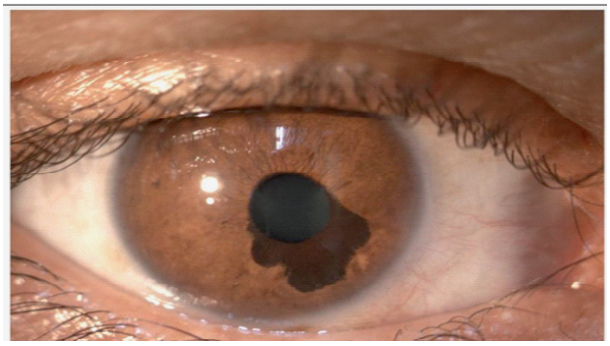

Fig. 2. Ectropion Uveae in a patient with NF1.

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