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**CASE REPORT**

# FOUR GENERATIONS IN A FAMILY WITH NEUROFIBROMATOSIS 1: PRECOCIOUS PUBERTY AND OPTIC NERVE TUMOR (OPT)

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A b s t r a c t: Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with varied clinical manifestations. The proband is a 6-year-old boy with signs of precocious puberty. His penis was 10 cm, testicles 8 ml, pubic hair P2-3, and the genital skin was hyperpigmented. Multiple cafe au lait spots well above 5 mm were noticeable on his skin, as well as hard subcutaneous nodules, mostly on his trunk. His intelligence and hearing are normal. He has no history of seizures. Laboratory analysis showed: LH LH 1.4 mIU/ml, FSH 6.2 mIU/ml, testosterone 183 ng/ml. Bone age was 9 years. LHRH stimulation was characteristic of true precocious puberty (LH 9.8 mIU/ml and FSH 8.9 mIU/ml after 30 minutes). The MRI of the brain showed a tumor of the suprasellar region with compression of the pituitary stalk. At present the boy is 6 years old and has been treated with triptoreline acetate for 3 months. The volume of the testicles has decreased to 7 ml and a slight loss of pubic hair was noted. In addition, his mother and his grandfather exhibited dermal masses, and focal cutaneous and subcutaneous growths. The great-grand father had had the same cutaneous changes and died at the age of 75 from unrelated causes. It has already been well documented that NF is associated with an increased risk of malignancy and precocious puberty. Hence, we emphasize the need for a close and regular clinical follow-up of the OPT, puberty and patterns of growth.

**Key words:** Neurofibromatosis 1, optic nerve tumor, precocious puberty, familiar occurrence.

## *Introduction*

Neurofibromatosis (formerly known as Von Recklinghausen's disease) belongs to a group of neurocutaneous syndromes, characterised by skin, nerve

and bone abnormalities. The inheritance is autosomal dominant with high penetrance and wide variability in expression. NF1 gene is located at chromosome 17q11.2. The NF gene presumably encodes a protein with tumour suppressor function. Precocious puberty and optic pathway tumours (OPT) are frequent complications of NF1. Indeed, precocious puberty influences the final adult height in NF1 patients, who were frequently found to have short stature and an abnormal growth pattern [1]. On the other hand, OPT is a condition that infrequently needs medical care and can significantly affect the quality of life and survival of NF1 patients [2, 3]. In total, the life expectancy of NF1 patients is shortened, given their propensity to develop malignancies [4].

We present a case of NF1 with precocious puberty and OPT. This patient is the fourth member of a family, with NF history in four generations. Moreover, the patient's mother has a ptosis on the left eye and a cerebral MRI hypodense zone.

## *Case report*

The proband was born after an uneventful pregnancy and delivery to healthy and young parents. At the referral (fig. 1), this six-year-old boy with normal intelligence, hearing and no history of seizures had signs of precocious

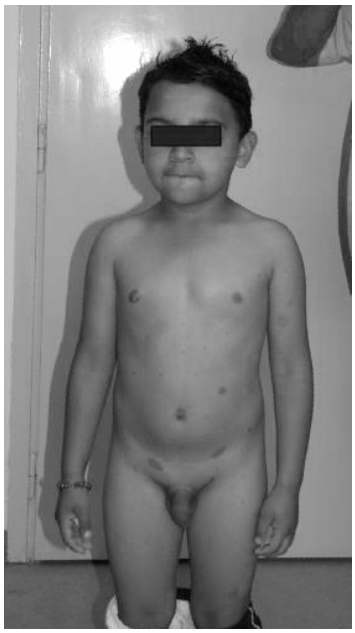

*Figure 1 – The proband, note the large cafe au lait spots and cutaneous prominences*
*Слика 1 – Пробанд со ѓолеми кафени дамки и кожни испаѝчувања*

puberty: his penis was 10 cm, testicles 8 ml, pubic hair P2-3, the genital skin was hyperpigmented. His skin had multiple cafe au lait macules well above 5 mm. In addition, there were hard subcutaneous nodules all over the body but more frequent on the trunk. His height was on the 50$^{th}$ percentile, bone age was 7 years. Initial tests showed: LH 1.4 mIU/ml, FSH 6.2 mIU/ml, testosterone 143 ng/ml, while the LHRH stimulation was characteristic of true precocious puberty (LH 9.8 mIU/ml and FSH 8.9 mIU/ml after 30 minutes). Ophthalmic investigation, including the visual fields, was uneventful. A tumour of the suprasellar region with impact on the pituitary stalk was found on MRI. The child has been treated with LHRH analogue for four months at the time of this manuscript. A slight decrease in the volume of the testicles (one ml) and slight loss of pubic hair was noted. Physical examination of his family (fig. 2) revealed that his mother and his grandfather have dermal masses, as well as focal cutaneous and subcutaneous growths. All other members of the family were without NF1 signs. Interestingly, the great-grand father had had the same cutaneous changes and died at the age of 75 years from unrelated causes.

*Figure 2 – The family, from left to right: the mother, the proband and his grandfather. Note the abundance of cutaneous changes in the grandfather relative to those in his daughter and in his grandson*
*Слика 2 – Фамилија со НФ1: од лево кон десно: мајка, пробанд, дедо*

*Discussion*

NF1 is notoriously variable in its clinical manifestations. In this family, the grandfather has mainly cutaneous changes, the mother ptosis, while the proband has precocious puberty and OPT.

Precocious puberty is frequently described in children with NF1 [2, 3, 5]. It has already been stressed that precocious puberty mainly occurs in association with optic pathway tumours [6, 7, 8]. However, occasionally it has been reported in the absence of optic gliomas [9, 10]. In fact, growth and puberty often present unusual patterns in NF1 [1]. In contrast to the precocious pubertal development a very high incidence of delayed menarche among NF1 girls has been reported [1]. Our patient fits into the category of children with precocious puberty and OPT.

Abnormalities in growth have also been reported. Virdis *et al*. 2003 [1] found a mean adult height close to the 25th percentile and final height that is significantly below the genetic target and predicted adult height. In addition, the shortest patients (< 10th percentile) were found to have a higher incidence of severe complications: CNS tumours, massive plexiform neurofibromas and severe scoliosis [1]. Short adult height was also reported by others [3, 11].

Optic pathway tumours are a frequent finding. Boulanger and Labrisseau 2005 [3] found optic glioma in 14.7% of the patients. Carmi *et al*. (1999; 11) found CNS pathology in 23/89 patients, while 6 patients required neurosurgery, and 2 patients cranial irradiation. Lama *et al*. (2007; 12) described 14 patients with OPT localized in the prechiasmal, chiasmal, prechiasmal/chiasmal and in the postchiasmal regions. Moreover, 4 patients had a massive involvement of the optic system, and one child had bilateral involvement of the optic nerves. Only 4/14 patients had partial and/or subtotal spontaneous regression. It was shown that the extra-optic location, tumour diagnosis in adulthood and symptomatic tumours are negative prognostic features [2]. Radiotherapy of OPT was associated with an important morbidity [2].

Cancer risk for patients with NF1 was recognized as increasedly early in the initial reports of NF1. NF1 patients were 34 times more likely to have a malignant neoplasm than persons without NF1 [4]. Their life-span is decreased: mean and median ages at death for persons with NF1 were 54.4 and 59 years, respectively, compared with 70.1 and 74 years in the general population [4]. Interestingly, the Cancer Genome Atlas Research Network (2008; 13) reported that NF1 was found to be an important gene in glioblastoma, with mutation or homozygous deletion of the NF1 gene present in 18% of tumours.

*Conclusions*

This is a description of a family with NF1 in which the NF1 history stretches over four generations. It is of note that the proband has an OPT, while the mother, although OPT–free, has a ptosis and a hypodense change on the parietal region at the MRI. It is to be stressed that both the growth and the evolution of the OPT have to be monitored closely. Their possible adverse effect on the quality of life and life expectancy is obvious.

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Резиме

## ЧЕТИРИ ГЕНЕРАЦИИ ВО ФАМИЛИЈА СО НЕУРОФИБРОМАТОЗА ТИП 1: ПРЕДВРЕМЕН ПУБЕРТЕТ И ТУМОР НА ОПТИЧКИОТ НЕРВ (ТОН)

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Неурофиброматозата тип 1 (НФ1) е автосомно доминантна болест со варијабилен спектар на клинички манифестации. Пробандот е 6-годишно момче со знаци за предвремен пубертет. Неговиот пенис има величина од 10 см, тестисите се 8 мл, пубичната влакнавост е П2-3, а кожата на гениталот е хиперпигментирана. На неговата кожа се гладаат повеќе кафени дамки, како и тврди подкожни нодули. Неговата интелигенција и неговиот слух се нормални. Неговиот ЛХ 1.4 мИЕ/мл, ФСХ 6.2 мИЕ/мл, тестостерон 183 нг/мл. Коскената старост е 9 години. ЛХРХ тестот беше во рамките на вистински предвремен пубертет (ЛХ 9.8 мИЕ/мл, ФСХ 8.9 мИЕ/мл по 30 минути). Магнетната резонанса на мозокот покажа тумор во супраселарната регија со компресија на питуитарното стебло. Во моментот пациентот веќе три месеци се лекува со трипторелин ацетат. Волуменот на тестисите се намали на 7 мл, и притоа настана мал губиток на пубичната влакнавост. Неговата мајка и неговиот дедо (од страна на мајката) исто така имаа дермални маси и кутани и субкутани израстоци. Прадедото ги имал истите кожни промени и починал на возраст од 75 години од причини неповрзани со НФ1. Ризикот од појава на предвремен пубертет и малигноми е добро документиран. Оттаму се наложува потребата за внимателно и редовно следење на промените на оптичките патишта, како и на карактеристиките на растењето и пубертетот.

**Клучни зборови:** Неурофиброматоза тип 1, тумор на оптичкиот нерв, предвремен пубертет, фамилијарна појава.

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