



Case report

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NEUROFIBROMATOSIS 1 IN TWINS - A CASE REPORT

SUMMARY

Von Recklinghausen's neurofibromatosis (NF-1) is the most common form of neurofibromatosis, accounting for 90% of cases. It is inherited in an autosomal dominant fashion and has the prevalence between 1 per 3000 and 1 per 5000, making it one of the most common autosomal dominant conditions in humans.

The paper reports a case of twins with neurofibromatosis-1 and anisomyopia with amblyopia in one of the children. Considering the poor sight due to anisomyopia in the examined twins, neurofibromatosis-1 was also discovered.

Ophthalmic examination is an essential part of the screening process.

Key words: neurofibromatosis (NF-1), twins

INTRODUCTION

The phakomatoses (from the Greek phakos, for "mother spot") are a group of disorders characterized by hamartomas of the skin, eye, and central nervous system. They were given their collective name by Van der Hoeve in 1932, who included neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau disease in the group.

There are usually four recognized forms of neurofibromatosis: *von Recklinghausen's neurofibromatosis* (neurofibromatosis type 1 [NF-1] or peripheral neurofibromatosis), *Bilateral acoustic neurofibromatosis* (neurofibromatosis type 2 [NF-2] or central neurofibromatosis), *Segmental neurofibromatosis* and *Cutaneous neurofibromatosis* (1).

NF-1 and NF-2 were independently documented in the historical literature. Mark Akenside provided a convincing account of NF-1 when "in the year of 1761, a man about threescore years of age came to St. Thomas hospital . . . he had been accustomed during the greater part of his life to

a constant succession of veins tumors that shot out in several places on his head, trunk, arms, legs, which indisposition he inherited from his father". In 1822 NF 2 was described in a young baker who was presented to the Scottish surgeon James Wishart with progressive deafness affecting both ears. He succumbed to septicemia after surgery for a cranial tumor, and postmortem identified multiple tumors of the dura mater and brain in addition to bilateral tumors of the eighth nerve (2).

Von Recklinghausen's neurofibromatosis (NF-1) is the most common form of neuro-fibromatosis, accounting for 90% of cases and presents in childhood. It is inherited in an autosomal dominant fashion and has a prevalence between 1 per 3000 and 1 per 5000, making it one of the most common autosomal dominant conditions in humans. The penetrance of NF-1 or the proportion of persons with the NF1 gene who show clinical evidence of the disorder is close to 100%, but because the mutation rate is so high, one half of newly diagnosed cases may represent new mutations. The gene has been

isolated to the proximal long arm of chromosome 17 (17q11.2) (1, 2, 3, 4).

According to the National Institute of Health Consensus Development Conference, at least two of the following criteria must be met to make the diagnosis of NF-1:

1. Five or more café-au-lait spots that are more than 5 mm in diameter in prepubertal patients; six or more café-au-lait spots that are more than 15 mm in diameter in postpubertal patients.

2. Two or more neurofibromas of any type, or one plexiform neurofibroma.

3. Axillary or inguinal freckling.

4. Optic glioma.

5. Two or more Lisch's nodules.

6. A distinctive osseous lesion (pseudoarthrosis of the tibia or sphenoid wing dysplasia) (1).

Café-au-lait spots are composed of epidermal melanocytes with giant pigment granules-macromelanosomes within the cytoplasm and are of neural crest origin. They increase in size and number up to the third decade, then, their number decreases. *Peripheral neurofibromas* are benign tumors consisting predominately of Schwann's cells and fibroblasts with endothelial, perineural, and mast cells, and may be cutaneous or subcutaneous. They appear as soft, gelatinous, mobile tumors, varying in size up to several centimeters and occur predominantly on the trunk. *Plexiform neurofibromas* are large, ill-defined subcutaneous swellings that are soft and "wormy" on palpation and pathognomonic of NF-1. It occurs in about one third of NF-1 cases, most commonly on the trunk and less often on the limbs and head and neck. *Mild cognitive impairment* is much more common and is manifested predominantly as visual-perceptual difficulty that increases in proportion to the severity of the disease (1).

Ophthalmologic assessment of patients with suspected NF-1 is important in order to confirm the diagnosis and to detect and treat potential ophthalmic complications. Proptosis and diplopia in NF-1 may be caused by orbital tumors - *optic nerve glioma*, *optic nerve sheath meningioma*, *orbital neurofibroma*. Patients with *chiasmal gliomas* may present endocrine abnormalities, hydrocephalus, visual impairment or nystagmus, but the majority of cases are asymptomatic and non-progressive. Others neural tumors include *neurilemmoma*, *plexiform neurofibromas* and *meningioma*. *Spheno-orbital encephalocele* is caused by the absence of greater wing of the sphenoid bone, due to congenital absence of part of the bone or erosion of the bone by orbital tumor. It characteristically causes a pulsating proptosis, unassociated with either a bruit or a thrill (1,3). *Eyelid neurofibromas* which may be either nodular or plexiform tend to develop early in life.

When involving the upper lid, they frequently cause a mechanical ptosis. *Lisch nodules* which are specific for NF-1 have been described as melanocytic hamartomas of the iris stroma and appear as tan to light brown nodules that stud the iris surface (5). *Congenital ectropion uveae* is uncommon and must be associated with glaucoma (3). Neurofibromas of the *conjunctiva* are rare, affecting only approximately 2% of patients with NF-1 and tend to affect the limbal conjunctiva. Diffuse thickening and neurofibromas of *corneal nerves* probably do occur in NF-1 and finally are *fundus lesions*: chorioidal naevimultifocal and bilateral are common and retinal astrocytomas are rare (1).

Investigation: CT scanning and MRI of the brain and orbits are important investigations in the management of NF-1. In addition, CT has been the investigation of choice for imaging optic nerve and chiasmal gliomas, but T2-weighted MRI imaging is superseding CT scanning in the investigation of both intraorbital and intracranial optic nerve gliomas. Assessment of visual evoked potentials is a useful noninvasive technique for determining optic nerve function and for monitoring progression or regression of chiasmal gliomas. Ophthalmic examination is an essential part of the screening process (1).

Case report

We report a case of nine-year-old twins, brother and sister, with neurofibromatosis type 1, anisomyopia and amblyopia in one child. Their mother brought them for examination at Orthoptics and Pleoptics Department of Ophthalmology Clinic in July 2002 for impaired vision and glance drifting noticed in the boy.

Ophthalmologically speaking, both children had anisomyopia, greater in brother, having poor vision in both eyes. The girl had subjective right visual acuity VAR = 0,8-0,9, left VAL = 0,7 - 0,8. With correction, it reached maximum on both sides, VAT = cc=1,0. Objective eye refraction (Sol. Homatropin 2%) indicated myopia astigmatism with differentiation in the major meridian lines from 0.25D for the right and 1 D for the left eye. The boy had poor visual acuity VAR= 3/60 and VAL = 2/60, with appropriate correction VAT = cc= 0,3-0,4 on both sides. Objective refraction indicated high myopia – myopia astigmatism, with differentiation in major meridian lines from 3,75D for the right eye and 3 D for the left eye. Reciprocal fixation was central in both children, with mild nystagmic movements in the boy. Hypertelorism was present in both children, but it was more expressed in the boy, who showed altering esophoria in the cover-uncover test and orthophoria in the girl; motility and convergence were normal in both children.

Biomicroscopic finding was clean, ophthalmoscopic finding matched myopia refraction in both children. Both of them were rather short for their age; the boy was slow during examination, mentally deficient with a pigment spot at the back of the head, about 2,5 cm in diameter, spotted while determining correction. By further examination, another spot, slightly over 20 cm, was found in the right armpit; on the calf it was smaller, café-au-lait in colour. They were also found on the sister's body, but less pigmented and smaller in size. Heteroanamnestically, mother of the children said that in four generations in her family there had been "such spots" on her relatives' bodies. After appropriate therapy and counseling for continuation of ophthalmologic treatment and check-ups, the children, under suspicion of neurofibromatosis, were sent to neurologist and pediatrician.

The reports of the control examinations confirmed the suspicion, Dg: Neurofibromatosis type 1 Nanosomia. BMI in girl was 22 kg, BH 122 cm; BMI in the boy was 21kg, BH 121,5 cm. A complete hormone status for both children was enclosed - it was within normal limits, cardiological and neurological findings were also normal, Rtg of the hands matched their maturity, US of abdomen, EEG normal for the girl. Thoracic kyphosis was noticed in the boy, so that he was sent to physiotherapy. By ultrasound of the heart, mitral valve prolaps regurgitation was found. Enalapril was recommended - 5 mg in the morning, while EEG recorded irritative temporo- parieto-occipital changes on both sides.

The children were followed during the five-year period by pediatrician, neurologist, orthopedist, and physiatrist. The last reports from December 2006 were satisfactory, considering expecting growth and incipient puberty signs, without growth disturbance and indications for further endocrinology examination; abdominal echo and EEG findings were normal in both children, but the brother is still having the physical treatment at home and cardiological therapy per os. Ophthalmologic findings from June 2007 for the boy are: poor vision with corrected visual acuity VAT= cc =0,5 and esophorim alternans. For the girl: better visual acuity VOT= cc 0,9-1,0 without strabismus. The children are still under regular control at Orthoptics and Pleoptics Department of our Clinic.

DISCUSSION

Neurofibromatosis-1 is the most common phakomatosis affecting approximately 1 person per 3500-4000 in general population. Men and women appear to be affected with equal frequency and there is no racial predilection for either type of the disease.

Many features of these syndromes do not appear until late childhood or early adulthood. The severity of the syndrome varies significantly from patient to patient. Many patients who have limited forms of NF are probably not identified (4).

The café-au-lait spots in this syndrome tend to be multiple, many are larger than 0,5 cm in diameter in childhood and enlarge to 1,5 cm in diameter by the postpubertal years. Six or more café-au-lait spots larger than 1,5 cm in diameter in postpubertal individuals are generally considered diagnostic of NF-1 (5). Axillary freckling and inguinal freckling are present in 90–95 % of affected individuals. Because of bone abnormalities related to the syndrome, some individuals develop severe scoliosis. NF-1 is rarely associated with frank mental retardation (1). About one half of the patients affected by NF-1 has some sort of learning disability, but most are of normal intelligence. In older patients, systemic hypertension appears to be more frequent than in the general population (4).

Ophthalmologic findings in NF-1 include Lisch nodules of the iris, subcutaneous pedunculated and plexiform neurofibromatosis of the eyelids, optic nerve gliomas, multifocal choroidal nevi and occasionally retinal tumors indistinguishable from the retinal astrocytic hamartomas (6). Lisch nodules are rarely present at birth, but tend to develop by the second to third decade of life in over 95% of persons who have NF-1 (4).

To summarise, Neurofibromatosis-1 is the most common phakomatosis in children. We reported a case of twins with neurofibromatosis - 1, and anisomyopia with amblyopia and strabismus in the boy. What is important is the analyses of refractive anomalies of the twins, particularly with myopia, poor sight due to anisomyopia, while the specificity of this case report is that neurofibromatosis-1 in children was discovered by considering poor sight. The myopic eye is generally considered to be a vulnerable eye and, at levels higher than 6 D, one that is especially susceptible to a range of ocular pathologies. Therefore, there is concern that the prevalence of myopia in young adolescent eyes has increased substantially over recent decades (7). The first report of refractive anomalies dates back to 1922 (8); the exact nature and interplay of genetic and environmental factors is not known and data suggest that environmental factors may interact with genetic factors to increase the risks of developing myopia. Future research is needed to identify specific modifiable lifestyle factors and genetic markers for myopia (9).

Ophthalmologic assessment of patients with NF-1 is important in order to confirm the diagnosis and to detect and treat potential ophthalmic complications.



Figure 1. Lisch modules



Figure 2. Café-au-lait spots in the patient

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NEUROFIBROMATOZA TIP 1 KOD BLIZANACA – PRIKAZ SLUČAJA

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SAŽETAK

M. Von Recklinghausen neurofibromatoza tip 1 (NF-1) je najčešća forma neurofibromatoze prisutna u 90% slučajeva. Nasledjuje se autosomno-dominantno sa prevalencom između 1 na 3000 i 1 na 5000 slučajeva, čineći jedno od najčešćih autosomno-dominantno nasledjenih stanja kod ljudi.

U radu su prikazani blizanci sa neurofibromatozom tip 1 i anisomiopijom sa ambliopijom kod jednog deteta. Sagledavanjem slabovidosti zbog anisomiopije kod ispitivanih blizanaca otkrivena je i neurofibromatoza tip 1.

Oftalmološka ispitivanja su esencijalni deo procesa skrininga.

***Ključne reči* : Neurofibromatoza tip 1, blizanci**