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NEUROFIBROMATOSIS TYPE I: A CASE REPORT

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ABSTRACT
Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disease that is characterized by the presence of multiple neurofibromas, café-au-lait spots and iris hamartomas. It is well established that the incidence of tumors in patients with NF1 is high compared with the normal population and that the majority of the tumors are non-epithelial neoplasms, including neurofibromas, malignant peripheral nerve sheath tumors, gliomas and leukemia. NF1 is underdiagnozed condition in Easter European countries as well in Lithuania. We report a family with type 1 neurofibromatosis cases. The diagnosis NF-1 was made according to the presence of diagnostic criteria of the National Institute of Health Consensus Development Conference.

INTRODUCTION

According to the European Union (EU) recommendations for the group of diseases classified as rare disease, this includes Neurofibromatosis, which occurs in less than 5 cases in 10,000 individuals. Neurofibromatosis Type-1 (NF1) is one of the most common autosomal dominant disorder that affects skin and nervous system. Occurring 1 in 2,500-3,000 individuals, regardless of their ethnicity, race or gender. Individuals with NF1 are born with one functional and one non-functional (mutant) copy of the NF1 gene in every cell of their body. Mutation that causes NF1 is located in 17q 11.2 of chromosome. Approximately half of all NF1 cases are being diagnosed in the absence of mutated gene in patient's family.

It is estimated that over 80% of newly occurring mutations of NF1 originates at early prenatal stages.

Furthermore, if an individual has NF1, there is 50% probability of mutated gene to be transferred.

NF1 distinguishing clinical features are variable manifestations. For this reason, patient demands clinical consultations and forecasts of different settings [1-3].

In 1882 Von Recklinghausen, who was a German pathologist, released scientific report that reviewed previous literature and described in detail Neurofibromatosis.

National Institute for Health Development Agreement conference

National Health Institute diagnostic criteria for 2 or more of the following clinical features of NF1 presence means to the patient.
Six or more cafe'-au-lait spots (0.5 cm in diameter) during the puberty, 1.5 cm after puberty;
Slag armpit or slag groin fields;
Two or more any type of neurofibroma;
Two or more iris Lisch nodules;
Specific bone disease;
First-degree relatedness to NF1 diagnosed person.
(Data from the National Institutes of Health)

CASE REPORT

Here is presented medical case where a 9 years old patient consulted a physician geneticist for painful subcutaneous grandson increased field, waist and bleached coffee discoloration of the skin.

Anamnesis

History of childhood evolution shows no clear features. During the first few years bleached coffee color stains on the skin are commonly observed. In the following 4-5th years nodules begin to appear on the skin. At the age

of 6-7 these nodules increase in size and tenderness accompanied by pain occurs.

Visual inspection

Asthenic morphology, slag armpits, bleached coffee stains (café-au-lait), color patches all over the skin (especially over the waist and on the buttocks) pigment spots on armpits.

Other signs:

Breath sounds heard over the lung tissue (vesicular breathing), arterial blood pressure is 115/70 mm Hg, heart rate 77 beats per minute. Hence heart rate is rhythmic and other systems show no pathological changes.

Genealogy:

The genealogy revealed that patient's family has no related diseases.

Research:

Laboratory tests: Complete blood count results: glucose, ESR, liver function tests are within normal limits. Patient underwent a lumbar subcutaneous node biopsy. Results have shown Neurofibroma.

Diagnosis was confirmed by neurofibromatosis diagnostic criteria.

Phenotypically: observed bleached coffee color stains (reliability of phenotypical observation is sufficient if there are more than 5 spots, which diameter is more than 5 mm). Damaged skin areas, including waist area, had been isolated.

This subcutaneous "tip of the nose" derivatives rigid consistency; the skin condition above remains the same; patient feels pressure; some of damaged areas are particularly painful.

Specific DNA testing (for specific gene mutation) was omitted as there are enough clinical evidence of Neurofibromatosis to be confirmed.

Final diagnosis: Neurofibromatosis Type 1. It is recommended to follow-up physical condition including persistent monitoring of damaged organs and those that are at risk. Hence visual assessment should be performed as patient could not complain of visual impairments.

Clinical signs

After being diagnosed with NF1, patients have to form a research and tracking plan in order that doctors could assess severity and progress of a disease. Children should be tracked teams: child neurologist, opticians, orthopedic traumatologist and others [4-6].

"Bleached coffee" color (café-au-lait) spots

Bleached coffee colored spots are visible at birth. They usually develop first few months since birth and 2 years at latest.

It is already known that early appearance of bleached coffee stains usually indicates NF1. Even though the amount of stains might vary from 1 to thousand, neither quantity nor size does associate with disease severity. It is important to mention, that size of stains is relevant to diagnose NF1. Hence, six stains with 0.5 cm in diameter until puberty or with 1.5 cm in diameter after puberty corresponds to 1 diagnostic criteria. Café-au-lait stains does not show any tendency of malignant transformation. In addition, there is no acknowledged evidence of use of laser therapy, hence cosmetic appearance of stains might be inhibited by disguising it externally.

Skin wrinkles slag

Axillary and inguinal slag (Crowe's sign) is mostly determined between 3-5 years of age. These slags are generally small (93 mm diameter). External slag covers the area above eyelids, neck, and under breasts. For some patients' slags may spread [6,7].

Lisch nodules

Lisch nodules are melanocytic iris hamartoma; notwithstanding Lisch nodules does not affect vision. This feature usually begins to appear to patients at age of 5-10, commonly identified by using slit lamp.

It is concluded that Lisch nodules are pathognomonic for neurofibromatosis and thus, their presence should be looked for in all suspected cases.

Neurofibroma

Neurofibromas' Schwann cells are a benign tumor that arise from the fibrous tissue around the peripheral nerve sheath and is composed of Schwann cells, fibroblasts, perineural cells and stem cells. NF1 lack of Schwann cells is considered as primary malignant tumor cells. Patients sometimes complain of localized neurofibroma itching or pain. Ferner et al. reported that antihistamines generally do not reduce the itch, other authors point out that localized itching can be treated with antihistamines. It is recommended to use emollient creams for skin to avoid irritation and excessive heat [7,8].

Despite the fact that there is no standard grading system, neurofibroma can be classified according to their appearance and location into 4 groups: focal or diffuse under the skin; subcutaneous, nodular or diffuse plexiform. Focal dermal or skin neurofibroma usually appears in late childhood or early adolescence and rarely causes pain or neurological deficits and generally do not transform into malignant tumors. NF1s' caused skin defects may lead patient to extreme discomfort and thus, it can be eliminated surgically.

Patients with NF1 should be warned about the risk of recurrence and hypertrophic scars after surgical removal.

Carbon dioxide laser treatment can be useful for removing small irregularities, but there is no proven benefit, which would underpin this treatment, compared

with the larger and more invasive surgical removal of neurofibroma. Subcutaneous neurofibroma removal can cause neurological deficits, and should be under the supervision of a qualified surgeon soft tissue tumors. These subcutaneous lesions can be detected palpitating the skin and may cause sensitivity or tingling along the affected nerve. Spinal neurofibroma may injure one or more nerve roots and may be connected both to the touch and with a motor neurological deficit [9,10].

Plexiform neurofibroma

Another major type of NF1 is referred as Plexiform. Plexiform neurofibromas are larger, more extensive tumors that grow from nerves anywhere in the body. Plexiform neurofibromas are often found in young children, sometimes even present around the time of birth. 30% of patients diagnosed with NF1 have Plexiform neurofibroma.

Plexiform neurofibromas' cells tend to expand into surrounding structures such as skin, fascia, muscle, bone tissue and internal organs.

Uncommonly, a plexiform neurofibroma may change into a cancer, called a malignant peripheral nerve sheath tumor (MPNST). Unfortunately, there are no reliable tests to screen for an MPNST.

Plexiform neurofibroma may be treated surgically. However, due to its' diffuse infiltrative nature, it is not possible to perform the full resection.

Damaged surface resection might be successful if it is made in early childhood. The latest volumetric MRI analysis has shown that Plexiform neurofibroma is growing rapidly in very first years of life. Hence, it is recommended to remove the surface of Plexiform neurofibroma in a young age [11].

Friedrich et al reported that early surgical intervention was well tolerated over a 3-year clinical and radiological tracking, no tumor regrowth evidence found. However, neurological deficit risks associated with removal of these tumors still promotes conservative current monitoring practices detailed fibroids conservative surveillance for possible malignant transformation in MPNST.

Malignant peripheral nerve Sheath Tumors (MPNST)

Malignant peripheral nerve sheath tumors (MPNST) develop in patients with underlying NF1, and usually arise as a result of malignant transformation of a pre-existing plexiform neurofibroma. Half of MPNSTs are associated with NF1, the autosomal dominant condition that, represents the most common human cancer genetic predisposition syndrome. Prognosis is generally poor, with high rates of relapse following multimodality therapy in early disease, low response rates to cytotoxic chemotherapy in advanced disease, and propensity for rapid disease progression and high mortality. [12]. Recent study with Fluorodeoxyglucose-positron emission tomography (FDG-PET) (which has been studied to evaluate the key clinical task of differentiating benign neurofibromas from MPNST in patients with NF1) has shown reliable and replicable differentiation with relatively high specificity. It is also important to bold importance of MPNST tumor resistance to chemotherapy and other systemic therapies.

Neurofibromatosis Neuropathy

It is important to distinguish sensory and motor disorders resulting multiple spinal neurofibromas.

Neurofibromatous neuropathy occurred in 1.3% of 600 patients with NF1. Its cause may be a diffuse neuropathic process arising from inappropriate signalling between Schwann cells, fibroblasts, and perineurial cells [12,13].

Skeletal dysplasia

Dystrophic scoliosis and tibial pseudoarthrosis are the most severe skeletal manifestations for which treatment is not satisfactory, emphasizing the dearth of knowledge related to the biology of NF1 in bone cells.

Symptoms: Bone lesions, low height, dystrophic scoliosis, tibia nonunion and sphenoid wing dysplasia.

Approximately 15% of individuals with NF1 tend to be below average in height. Scoliosis is found in 10-25% of patients with NF1 [14].

NF1 children need yearly assessment of the spine. It is recommended to use brace for progressive scoliosis to reduce pain, improve stability and prevent disease progression. In more severe cases, such as dystrophic scoliosis, patient may require surgery. Dystrophic scoliosis, the most difficult form, characterized by early onset, rapid progression. This severe form affects less than 10% of NF1 individuals. This may lead to spinal cord compression.

Sphenoid dysplasia or typical long-bone abnormalities such as arthrosis are common among NF1 individuals.

Congenital dysplasia of the tibia pain gets flexure legs to the side. Distinguished cortical bone loss that far in advance makes it possible to cause pathological fractures in the first year of life. Re-fracture and failure to heal can result in nonunion (artificial joint). Pseudarthrosis operations generally ineffective, partly because of weakened secondary localized healing response osteopenic. Early treatment with bisphosphonates gave positive results [15]. In the localized osteopenia, patients with NF1 exhibits a total bone mineral density reductions. Sufficient bone mass is the most important determinant of bone health in adults [16,17]. Sport mode in children, which aims to improve bone strength is of paramount importance [15]

Optic nerve glioma (OPG)

An estimated 15-40% of children with NF-1 have optic nerve glioma or visual pathway gliomas involving the optic nerve, chiasm, or optic tract. Some of these lesions

are asymptomatic. Optic nerve gliomas are locally invasive and slow growing with low malignant potential. However, chiasmatic gliomas may invade the hypothalamus and third ventricle, causing obstructive hydrocephalus.

OPG is found in 15% of children with NF1 and usually occurs in the first decade of life. Most NF1-associated OPGs have a benign course, and only one third to one half of patients with NF1 with an OPG develop visual symptoms. Symptomatic OPGs can cause proptosis, vision loss, and early puberty. Compared with symptoms related to accidental OPGs, NF1-associated with OPGs symptoms usually manifest as early puberty, and intracranial pressure symptoms are less common.

The risk of symptomatic OPG is greatest in children under 7 years, and older individuals rarely develop tumors that require medical intervention children do not complain of visual impairment until it is advanced and sometimes only when they have bilateral visual loss.

Specialist advice is essential for the management of OPG and therapy is usually with vincristine and cisplatinum. Occasionally surgery is warranted to deal with severe proptosis or to debulk extensive chiasmal gliomas. Radiotherapy is not advocated in young children because of potential second malignancy, neuropsychological, vascular and endocrine consequences. Rapamycin reduces astrocyte growth in vitro and might have a future therapeutic role in the management of OPG.

Baseline MRI to detect asymptomatic OPGs not indicated. Annual neurooftalmologinis asymptomatic cases is crucial for tracking diagnosed NF1 patients. Progressive disease is less common as random OPGs, and treatment initiation should patients. Glioma, can also occur in the brain stem gaskets cerebrum and cerebellum, but is rare - up to 3.5% of patients with NF1 [17].

Cardiovascular malformations

NF1 cardiovascular manifestations include congenital heart disease, hypertension and vasculopathy. Coronary heart disease occurs more often than expected compared to the general population,with pulmonary artery stenosis, forming 25% of all cases of cardiovascular problems.

It is recommended to follow-up heart condition by frequent its monitoring using auscultation and blood pressure measurement. Any slight murmur should be evaluated. Cerebrovascular disease, especially in younger patients, usually occurs in stenosis or occlusion and is diagnosed most often in children who have clinically manifested weakness involuntary movements, headache, or convulsions. secondary to ischemia. Any patient who has a sudden onset neurological disorder should be assessed cerebral blood flow.

Hypertension is significantly associated with alteration NF1 population mortality and blood pressure should be tested annually for maintaining it <140/90 mm / Hg. Renal artery stenosis is the most common cause of hypertension in patients with NF1, especially in the pediatric population. However, it is important to perform differential diagnosis of coarctation of the aorta and pheochromocytoma. Pheochromocytoma occurs from 0,1-5,7% of individuals with NF1.

Neurocognitive deficits

Neurocognitive deficit commonly occurs as a complication of NF1.

In addition to the specific non-verbal and verbal language deficits (found in 30-65% of children with NF1) are characterized by small and large motor coordination deficits. NF1 cognitive phenotype is marked by greater attention deficit / hyperactivity disorder (ADHD), autism spectrum disorders, behavioral anomalies, and psychosocial issues. While receiving advanced care, children with ADHD usually respond well methylphenidate therapy. Furthermore, it is recommended to supply cognitive behavior therapy. Patients with NF1 IQ levels tend to fall into the low average range.

CONCLUSIONS

It is necessary to clarify as soon as possible new cases of disease as a diagnosis of NF1, any special disease surveillance and treatment plan, targeted genetic counseling of family members and the state level, appropriate treatment and prevention measures planning.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committeeand with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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