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Pediatric Neurofibromatosis Type 2: A case report.

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Abstract

The monitoring of a medical case of a rare genetic neurocutaneous disease - neurofibromatosis type II in a child of 6 years is presented. There is no full-scaled picture of the disease probably due to the patient's age, but at the same time a histologic pattern and molecular genetic diagnosis confirm it. Literature data is given, questions of hereditary of the disease, a clinical picture and possible diagnosis are discussed.

Keywords: neurofibromatosis type II, neurofibroma, schwannomas, NF II gene, de novo mutation.

Introduction: Hereditary skin diseases are one of the topical sections of pediatric dermatology, since they are often accompanied by damage not only of the skin, but also of other organs and systems of the body.

Neurofibromatosis type II is genetically determined disease characterized by polysystemic damage involving nervous and skeletal systems, organs of hearing and sight, skin and internals. This pathology is accompanied by increased risk of malignant tumors arising from gene mutation of NF II with autosomal dominant inheritance [1,2]. Incidence of the condition is about 1 in 60,000[1,2,3].

We give own observation of Neurofibromatosis type II in a child who has diffusely located tumor mass on the skin, hypopigmented patches, localized hypertrichosis. There is no full-scaled picture of the disease probably due to the patient's age, nevertheless the early detection this pathology is extremely important because of conceivable concomitant hearing disorder.

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Our clinical case: A six-year-old boy was under observation. At the age of one year, child's parents noticed hypopigmented patches on his back. A dermatologist suspected vitiligo, but no treatment was given. At the age of 18 months, mass lesions began to appear on various parts of his body (right side of the trunk, right buttock, left palm, and left knee). The parents applied to a dermatologist in the department of pediatric dermatology of the State Scientific Center of Dermatovenereology and Cosmetology where provisional diagnosis of neurofibromatosis was made. The patient was recommended histological examination of tumor mass of the skin, consultations of geneticist, ophthalmologist, neurologist and orthopedist.

Family history: The boy's parents are not consanguineous and have no hereditary diseases. The proband has a healthy brother.

Patient's phenotype: Height 115 cm; weight 19.5 kg; neuropsychological development consistent with his age; no signs of abnormal embryogenesis.

Status localis: Irregular, oval hypopigmented macules with poorly defined borders measuring 3 to 5 cm are present on the skin of the back, chest and left knee. Wood's lamp examination of the macules did not reveal snow-white fluorescence. Soft and elastic masses, measuring 0.4 to 1.5 cm, are observed on the mucosa of the lower lip and that of the tongue, under the skin of the left palm, and in the area of the left knee, right buttock, and right side of the trunk (Fig.1). Some masses are with local hypertrichosis (Fig.2). The overlying skin is pale pink. These masses are not adherent to the underlying tissues, are non-tender, and are not associated with any subjective discomfort.

Excisional biopsy was perfomed and submitted (Fig. 3, 4). The magnetic resonance imaging of the brain and spinal cord was recommend and perfomed as well a genetic study.

Histology:
Gross examination: A piece of skin with underlying subcutaneous fat measuring 2 × 1.5 × 1 cm overall.
Microscopic examination: The epidermis is of normal thickness with signs of compact hyperkeratosis. An unencapsulated nodule with poorly defined borders, composed of bundles of spindle cells, with S-shaped nuclei oriented in different directions, is seen deep in the dermis. Some of the cells are in arrangements forming structures similar to nerve trunks. Immunohistochemistry with anti-calretinin antibodies reveals positive staining of some cells inside the nodule . Diagnosis: neurofibromatosis Type 2

Diagnostic Tests

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Magnetic resonance imaging of the brain: No signs of space-occupying or focal lesions, no changes consistent with contusion and/or injury, and no hematomas were observed within the brain.

Genetic study: A heterozygous mutation was found in the exon 8 of the NF 2 gene (Chr22: 30057302, rs 74315496).

Discussion

Neurofibromatosis type 2 is a genetically determined, multi-system disease of the nervous system, skin, internal organs, eyes, and skeleton, and is associated with increased risk for malignancies caused by a mutation in the NF2 tumor suppressor gene, which follows an autosomal dominant inheritance pattern. It affects on average 1:60000 people in the general population. [1,3]

Neurofibromatosis type 2, or central neurofibromatosis, is clinically less often manifested by cutaneous tumors (schwannomas) and is typically associated with bilateral vestibular schwannomas of the cranial or peripheral nerves, astrocytomas, and intracranial and/or spinal meningiomas. [4]

The classification of neurofibromatosis type 2 involves three main types, based on clinical manifestations and severity of symptoms: the Wishart, Gardner, and mosaic types.[4,5]

The Wishart type presents in childhood or young adulthood (typically before 25 years of age). Patients develop bilateral vestibular schwannomas associated with multiple spinal tumors, and the disease progresses relatively quickly. [6]

The Gardner type manifests itself at an older age (after 25 years) as a milder disorder, associated not only with bilateral schwannomas but also with a small number of meningiomas. [7,8]

Mosaic neurofibromatosis type 2 is the mildest type; it is caused by postzygotic mutations, meaning that only some cells have a mutation in the *NF2* gene. In about 20-35% of cases, mosaic neurofibromatosis type 2 is a *de novo* disorder. [8]

In one-third of the patients, one of the first manifestations of neurofibromatosis is vestibular schwannomas. In adults the initial symptoms include unilateral partial or complete hearing loss or tinnitus, which is caused by damage to the eighth cranial nerve (CN VIII); in children, however, the onset of the disease is not associated with vestibular dysfunction. [7,8]

In children the disease may initially present clinically with cutaneous tumors or vision problems. In only 15-30% of children with neurofibromatosis type 2, are the initial symptoms caused by vestibular schwannomas. [8]

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Skin lesions are most often seen in pediatric patients and include pigmented or hypopigmented macules, slightly elevated intradermal lesions, commonly associated with hypertrichosis, and subcutaneous lesions occurring along peripheral nerves. [6,7,8]

Our clinical case has the distinctive features of manifestations of type II neurofibromatosis in children. The first clinical manifestations in our patient were pigmented and hypopigmented spots. After that intradermal lesions with local hypertrichosis, towering above the level of the skin, formed along the peripheral nerves had sprung up.

The standard instrumental method for diagnosing neurofibromatosis type 2 is magnetic resonance imaging of the brain and spinal cord, which can detect small lesions at early stages of the disease. The absence of changes in magnetic resonance imaging in our patient may be due to early childhood.

Clinical examination includes the patient's medical and personal history, neurological and ophthalmological examinations, genetic evaluation, molecular genetic analysis, and assessments by an ENT and an audiologist. [9,10]

Our patient had a molecular genetic study of the genes NF 1 and NF 2, where a heterozygous mutation was found in the exon 8 of the NF 2 gene (Chr22: 30057302, rs 74315496), which leads to the premature termination of translation at the codon 262 (p. Arg262Ter, NF2: NM_000268). This variant of mutation in the heterozygous state leads to the development of type II neurofibromatosis (OMIM: 101000).

Neurofibromatosis type 2 remains poorly understood, with only a handful of cases reported in the literature. Given the patient's medical history, phenotype, specific clinical features, local manifestations, and results upon examination, such cutaneous lesions can be considered initial signs of neurofibromatosis type 2, especially in a patient of preschool age with a mutation in the *NF2* gene.

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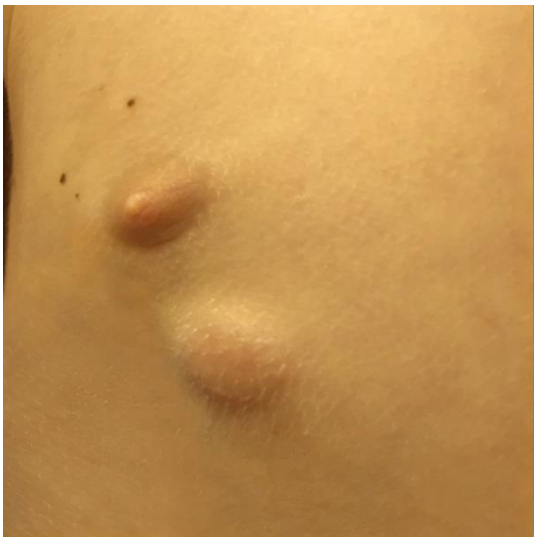

Figure 1.Right lateral trunk schwannoma.

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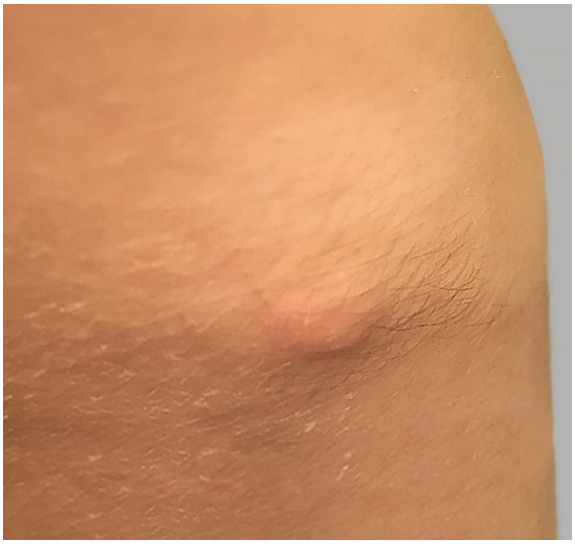

Figure 2. Hypopigmented patch, left knee schwannoma with localized hypertrichosis.

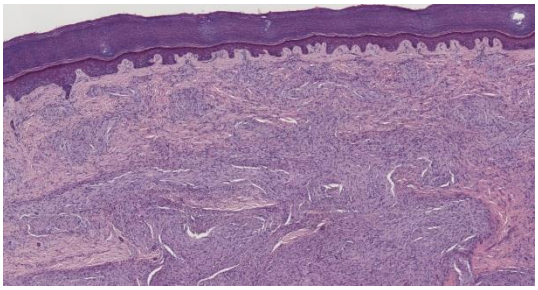

Figure 3. Histologic pattern of node in the palm area. Intradermal nodes with no clear boundaries, HE stain, x 40

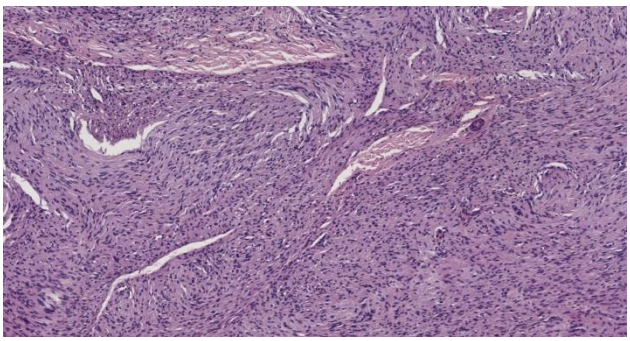

Figure 4. Histologic pattern of node in the palm area. Fascicles of fusiform cells with S-shaped, HE stain, x 200