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TYPE 1 NEUROFIBROMATOSIS: CLINICAL, PATHOLOGICAL AND RADIOLOGICAL CORRELATION

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SUMMARY – Type 1 neurofibromatosis is a phacomatosis inherited as an autosomal dominant disorder. It is characterized by the occurrence of hamartomas and tumours on the body, particularly on the nervous system and skin. The clinical criteria for its diagnosis include the following findings: six or more café-au-lait spots of æ5 mm in diameter on the skin, two or more neurofibromas, spots in the axillary or inguinal region, optic nerve gliomas, two or more hamartomas of the iris, and characteristic changes of bones and brain. The pathologist's finding is predominated by the occurrence of neurofibromas along peripheral and cranial nerves, optical gliomas, policystic astrocytomas of the brain, and hamartomas of the brain and iris. During a 15-year period, 166 children with type 1 neurofibromatosis were examined and radiologically evaluated. Classical radiological bone x-rays were made, along with brain and spine CT and MR. Dysplasia of the greater wing of the sphenoid bone was detected on bone tissue accompanied by deformation of the orbit and middle cranial fossa, wedge-formed vertebrae, expanded intervertebral foramina, and cystic masses in other bones. In the brain parenchyma, hamartomas, policystic astrocytomas and optic nerve gliomas were detected along with neurinomas of the cranial and spinal nerves. Based on the clinical, laboratory and radiologic follow-up of the patients with type 1 neurofibromatosis, the need is stressed for a multiple approach to the diagnosis and treatment of neurofibromatosis.

Type 1 neurofibromatosis (von Recklinghausen neurofibromatosis) is a phacomatosis inherited as an autosomal dominant disorder. It is characterized by the occurrence of hamartomas and tumors on the body, particularly on the nervous system and skin[1].

Neurofibromas can be plexiform, solitary, or skin nodular. They occur as optic nerve gliomas, rhabdomyosarcomas, pheochromocytomas, carcinoids, harmatomas of iris comprising melanocytes (Lisch nodules), and multiple café-au-lait spots caused by the increased number of melanocytes in the basal epidermal layer.

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Typical changes in bones are sphenoid bone dysplasia and loss of cortex thickness in long bones with/without fractures and bending. Pseudoarthrosis and scoliosis are frequently detected in long bones. The developing tumors have the capacity of malignant alteration. The clinical findings might include growth failure with macrocrania, epilepsy, and milder form of mental retardation, learning impediments, speech development problems, endocrine disturbances such as precocious or delayed puberty and congenital adrenal hyperplasia.

According to the National Institutes of Health (NIH) Consensus Development Conference Statement[2], the clinical criteria for the diagnosis of neurofibromatosis include:

1. six or more café-au-lait spots of æ5 mm in diameter on the skin in pre-puberty, and of æ15 mm in diameter in postpuberty patients;

2. two or more neurofibromas of any type or one plexiform neurofibroma;
3. spots in axillary or inguinal region;
4. optic nerve glioma;
5. two or more Lisch nodules (hamartomas);
6. characteristic changes on bones, such as sphenoid bone dysplasia or loss of long bone cortex thickness with/without pseudoarthrosis; and
7. first relative with NF1 diagnosed according to the above criteria.

The diagnosis is set when two or more of the above conditions are met. Although the café-au-lait spots are considered a typical sign, they are not a pathognomonic sign since they can also indicate other diseases. The spots are the first indication and can be found at the child's birth; later, they become numerous, stationary or reduce in number and pigmentation grade in adult age. The spots are of melanocytic origin, varying in size and localization.

Peripheral neurofibromas are clinically differentiated as cutaneous and subcutaneous. Cutaneous neurofibromas located inside the dermis and epidermis look like small nodules, 0.1 to 2 cm in diameter. They move with the skin, have soft consistency, and dark red or violet color. Subcutaneous neurofibromas originate from larger nerve roots, and they are subcutaneously palpable as nodules of firmer consistency[3].

Plexiform neurofibromas that extensively grow along large peripheral and cranial nerves and plexuses extensively encompass the skin and neighboring subcutaneous and deeper tissues (bone, paraspinal structures, mediastinum, retroperitoneum, visceral organs), look like large subcutaneous tumors of soft to pastous consistency inside which multiple nodes and hypertrophic nerve bundles of well defined edges are palpable. The skin over plexiform neurofibroma is changed, thickened and hyperpigmented with excessive hairiness.

Optical gliomas are poorly differentiated pilocytic astrocytomas[4].

Lisch's nodules or hamartomas of the iris are asymptomatic iris tumors. They mainly occur between 5 and 10 years of age. The nodules are avascular melanocytic, dome-shaped tumors with transparent to yellowish smooth surface, jelly-like, up to 2 mm in size, located in the iris.

Neuroglial lesions are cutaneous or subcutaneous neurofibromas involving eyelids, of tan to violet color. They occur in late childhood, and their number increases in adolescence and adult age.

Type 1 neurofibromatosis is typical for bone changes in the skull, with a finding of unilateral defect of the small or great wing of the sphenoid bone or hypoplasia with elevation in the small wing of the sphenoid bone and loss of posterosuperior orbital wall with consequential increase in the orbit size and enlargement of the upper fissure, along with the possible finding of enlargement of the optic nerve canal. The sphenoid bone defect and defect in the junction of the parietomastoid and occipitomastoid suture in the left side of the skull, along with poorer development of the mastoids and hypoplasia of the maxillary and ethmoid sinuses result in facial deformity.

The spine is scoliotic, the vertebral bodies are rotated with lateral subluxation, wedged, with indented and concave dorsal edge, erosion changed pedicle, enlarged foramina, with thinned and spined transverse processes and ribs[5].

Long bones are bent, exposed to fractures that heal in defect rather than in normal callus accompanied by pseudoarthrosis. The tibia is involved while the fibula is usually hypoplastic[6].

The bone changes are usually cystic, and cysts are located subperiosseously and intraosseously. Intraosseous changes include indentations and impressions in cortical surface caused by mechanical pressure of the surrounding neurogenous cells, and focal hemorrhages under the poorly adhering and dysplastic periost. Intraosseous cystic lesions are caused by direct invasion of the periost, cortex and Haversian canals by neuro-fibromatous cells. Changes in growth are caused by premature closing of epiphyseal plates or excessive growth of bones and soft tissue, and may occur individually or jointly in different combinations, which causes partial gigantism[7].

The fact that in more than half of all patients with type 1 neurofibromatosis pathologic brain and orbit changes were detected in some studies, makes magnetic resonance a leading radiologic method for evaluation of changes caused by type 1 neurofibromatosis[8]. Hamartomas and neoplastic lesions, including optic nerve and brain parenchyma, are visualized on magnetic resonance as multifocal changes with high signal intensity in T2 image of the brain stem, cerebellar and cerebral white matter, basal ganglia, optic nerve and optic pathway. Although they are not fully histologically explained, these "white" lesions in T2 image are considered to be a consequence of abnormal myelinization or dysplastic glial proliferation, so they are considered hamartomas[9]. Radiologic criteria for differentiation of this lesion from tumor are based on the lack of displacement of the surrounding anatomic structures

and lack of vasogenous brain edema. Increased signal intensity after administration of a paramagnetic contrast, such as found in tumors, is not a completely reliable sign because it could be an indication of hamartoma. Exceptions are, sometimes, lesions in globus pallidus that cause very high signal intensity in T1 imaging. It is believed that these completely atypical signals are the consequence of the increase in the number of myelocytes or melanin ectopia.

Optic nerve gliomas, particularly in childhood, are a significant, important and frequent diagnostic finding. Approximately 2% to 5% of all brain tumors in children are optical gliomas, and about 7% of patients with optic nerve glioma will have type 1 neurofibromatosis. Histologically, optic nerve glioma is a pilocytic astrocytoma with the highest incidence in optic chiasm, more rarely detected intraorbitally. On magnetic resonance, it is visualized as a completely thickened and tortuous tumourous nerve. When this change is bilateral, the diagnosis of neurofibromatosis is almost certain. Although in most cases these tumors grow progressively, cases have been recorded of their reduction, so the opinions on the optic nerve glioma treatment are controversial[10].

Many authors believe that, considering their growth, these tumors behave like hamartomas rather than real neoplasms. Thus, a conservative treatment of glioma in neurofibromatosis is sometimes recommended, while in most cases the final decision on surgery is delayed as long as vision persists[11]. The radiotherapy value is also uncertain because increased tumorigenesis in phacomatoses could cause generation of new tumors.

Contrary to optic nerve glioma, gliomas in the brain parenchyma (non-optic gliomas) are more rare and most frequently located in the brain stem, lamina tecta and around the aqueduct. From the radiologic standpoint, these are the lesions that reveal displacement in the surrounding anatomic structures, vasogenous edema and post-contrast imbibition, which makes their differentiation from hamartoma possible.

One third of the patients with neurofibromatosis show neurofibromas located subcutaneously or along the cranial nerve, most frequently in the nervus trigeminus branches. They are often coupled with dysplasia of the greater wing of the sphenoid bone and changes in the central cranial fossa, which is a frequent site of arachnoid cyst formation. On magnetic resonance, they are imaged as a spindle-shaped tumor along the nerve, and after administration of a paramagnetic contrast medium they show contrast enhancement[12].

The complete spine must be imaged, because they also occur on spinal nerves together with meningocele, cause dilatation of intravertebral openings and frequently extension of paravertebral soft tissues.

During a 15-year follow-up of 166 children with type 1 neurofibromatosis (NF1), all relevant clinical, laboratory and radiologic examinations demanded by the multidisciplinary approach to the diagnosis and treatment of patients with neurofibromatosis were performed. Based on the results obtained, the patients were classified according to Riccardi in four disease severity stages: stage 1: mildest (skin changes – café-au-lait spots, spottiness, simple neurofibromas); stage 2: mild complications (mild scoliosis, precocious puberty, behavioral disorders); stage 3: moderate complications (need for palliative treatment and follow-up – hemihypertrophy, controlled epileptic seizures, intestinal involvement); and stage 4: massive sensory and motor symptoms (intracranial, spinal tumors, severe mental retardation, severe scoliosis, uncontrolled epileptic seizures)[13,14].

The treatment of these patients is mostly symptomatic, but it demands multiple clinical follow-up with at least one annual examination aimed at an early detection of complications.

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Sažetak

NEUROFIBROMATOZA TIPA 1: KLINIčKA, PATOLOGIJSKA I RADIOLOGIJSKA KORELACIJA

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Neurofibromatoza tipa 1 je fakomatoza koja se nasljeđuje autosomno dominantno, a obilježena je pojavom hamartoma i tumora po tijelu, poglavito živčanog sustava i kože. Klinički kriteriji za postavljanje dijagnoze temelje se na nalazima: šest ili više pjega boje bijele kave promjera vežeg od 5 mm na koži, dva ili više neurofibroma, pjegavosti pazušnih i ingvinalnih regija, optičkog glioma, dva ili više hamartoma šarenice i znakovitim promjenama na kostima i mozgu. U nalazu patologa dominira pojava neurofibroma duž perifernih i kranijskih živaca, optičkih glioma, policističnog astrocitoma mozga te hamartoma mozga i šarenice. U tijeku 15-godišnjeg razdoblja pregledano je i radiološki obrađeno 166 djece s neurofibromatozom tipa 1. Primijenjene su klasične radiološke metode snimanja kostiju, CT mozga i kralješnice te MR mozga i kralješnice. Na koštanom tkivu utvrđena je displazija velikog krila sfenoida pražena deformacijom orbite i srednje lubanjske jame, klinasto oblikovani kralješci, prošireni intervertebralni otvori te cistične tvorbe u dugim kostima. U parenhimu mozga utvrđeni su hamartomi, policistični astrocitomi i gliomi optikusa te neurinomi kranijskih i spinalnih živaca. Na temelju kliničkog, laboratorijskog i radiologijskog praženja bolesnika s neurofibromatozom tipa 1 ukazano je na potrebu višestrukog pristupa u dijagnostici i liječenju neurofibromatoze.