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Specific features of orthopedic pathology in neurofibromatosis type I patients of the Republic of Bashkortostan

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Abstract

Background Neurofibromatosis type 1 (NF-1) is a hereditary tumor syndrome characterized by cutaneous, subcutaneous and plexiform neurofibromas, optic nerve gliomas, cognitive disorders and can be associated with orthopedic pathology. Clinical manifestations of NF-1 include skeletal abnormalities requiring a specific approach to treatment of the tumor-like processes in the involved bones and joints.

The **objective** was to determine the frequency of orthopedic pathology and clinical manifestations of the disease in NF-1 patients seen in the Republic of Bashkortostan (RB) and make international comparisons.

Material and methods Outpatient records of patients with a clinical diagnosis of NF-I, the results of laboratory and instrumentation studies were examined. A retrospective analysis of the frequency of occurrence of the main clinical manifestations of NF-1 and orthopedic pathology was conducted. An interactive 2 × 2 contingency table was used for calculation of association statistics (Pearson χ^2 criterion) with the Yates correction for continuity developed by V.P. Leonov and four-field contingency tables were analyzed.

Results and discussion The incidence rate of NF-1 was 1:7407 by 2024 in the RB, which is 2.3 times less than the world average (1:3000 people). Associated malformations included scoliosis seen in 17.4 %, chest deformity observed in 5.3 %, pseudoarthrosis in 3 %, facial dysmorphism in 9 %, short stature in 13.8 % of patients. Osteoporosis, facial asymmetry and sphenoid wing dysplasia were not observed in NF-1 patients in the region. A statistically significant difference in the frequency of occurrence of orthopedic pathology was determined in patients with NF-1 from the RB using four-field contingency tables. A retrospective analysis showed a statistically lower incidence of orthopedic pathology in NF-1 patients of RB as compared to the world average which indicated the need to include orthopedic consultation in medical and economic standards for the timely detection of pathology and treatment.

Conclusion Analysis of orthopedic pathology in NF-1 patients from RB showed the occurrence of chest deformity, scoliosis, short stature and pseudoarthrosis being comparable with world data. Skeletal anomalies, facial dysmorphism and macrocephaly were not common for NF-1 patients of RB. No cases of osteoporosis, facial asymmetry and sphenoid wing dysplasia being characteristic of NF-1 patients were detected in the patients. Learning difficulties were more common for NF-1 patients with orthopedic pathology as compared to NF-1 patients of RB.

Keywords: chest wall deformity, neurofibromatosis type 1, osteoporosis, pseudoarthrosis, scoliosis, frequency of occurrence

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INTRODUCTION

Neurofibromatosis includes three main types which are distinct genetic disorders: neurofibromatosis type 1 (NF-1), neurofibromatosis type 2 and schwannomatosis. NF-1 is a monogenic disease caused by heterozygous mutations in the *NF1* tumor suppressor gene located on the long-arm 17 chromosomes (17q11.2) [1]. According to meta-analysis [2], NF-1 occurs with an average frequency of 1:3,164 of the population worldwide, varying from 1 in 2,020 to 1 in 4,329 in different populations. NF-1 pooled birth incidence was 1 in 2,662 (1 in 1,968-1 in 3,601). About half of NF-1 cases are familial, due to transmission of the disease to the next generation in an autosomal dominant manner. The other half of NF1 cases arise from a new, spontaneous mutation (a de novo mutations) in the *NF1* gene [3]. NF-1 is a hereditary tumor syndrome characterized by multiple café-au-lait macules (CALM) with a diameter of more than 5 mm in prepuberty and more than 15 mm in postpuberty with 99 % being melanocyte tumor growths in the skin due to loss of heterozygosity in the *NF1* gene [4], iris hamartomas (Lisch nodules), cutaneous and subcutaneous neurofibromas, optic gliomas, and plexiform neurofibromas. NF-1-specific bone dysplasias include congenital pseudoarthrosis and/or cortical thinning of long bones, sphenoid dysplasia, spinal deformity (scoliosis/kyphoscoliosis) and chest deformity (pectus excavatum/keeled chest) [5]. According to the criteria developed by the National Institutes of Health (NIH) the diagnosis of NF-1 can be established clinically with both of the signs detected. One sign of the disease would be sufficient in the presence of a confirmed case of NF-1 in genetic relatives [6].

Tumor manifestations are most common manifestations in patients. CALM is detected in 96.5 % of NF-1 patients, freckling of the axillary and inguinal areas is observed in 90 % [7]. Cutaneous and/or subcutaneous neurofibromas are detected in more than 99 %, hamartomas of the iris seen in 70 %, plexiform neurofibromas observed in half of NF-1 patients [6]. Brain damage is also characteristic for NF-1 with optic nerve gliomas seen in 27 % of the cases, brain tumors in 10 %, hydrocephalus in 7.7 % [8], and epilepsy in 8.1 % [9]. Severe complications of NF-1 include malignant peripheral nerve sheath tumors (MPNST) seen in 13 % of NF-1 patients as a result of the degeneration of plexiform neurofibromas; the patients are characterized by high mortality [10].

In addition to the tumor manifestations of NF-1, all patients experience diffuse, lifelong cognitive impairment, leading to learning difficulties in 40 % of cases [3], and common injury to the musculoskeletal system (MSS). According to a meta-analysis [11], approximately 26.6 % of NF-1 patients have scoliosis that usually develops in early childhood affecting the thoracic spine. No reliable correlation has been found between scoliosis and the NF-1 genotype. On average, 24 % of NF-1 patients have short stature [12], and 5 % have pseudoarthrosis [6] which results from fibrous hamartomas of long bones with the lost heterozygosity of the *NF1* gene in the tissues [13]. In total, skeletal anomalies are observed in at least 60 % of NF-1 patients with severe cases requiring surgical treatment [14]. Treatment of pseudoarthrosis in NF-1 would include excision of fibrous hamartoma tissues and subsequent correction using the Ilizarov external fixation [13]. Spondylodesis and the growing rods were practical for treatment of scoliosis in NF-1 patients [11].

Sphenoid wing dysplasia characteristic of NF-1 can be detected in 9 % of the patients, facial asymmetry in 10 %, macrocephaly in 25 % [15], and skull anomalies leading to facial dysmorphism in 53 % of NF-1 patients [16]. Chest deformity is detected in 3.5 % of NF-1 patients, which is significantly higher than in the general population (0.3 %) [17]. A meta-analysis [18] showed that NF-1 can be associated with decreased bone mineral density in the lumbar spine and femur and an increase levels of parathyroid hormone and C-telopeptide of type I collagen in the blood, a decrease in alkaline phosphatase, calcium, vitamin D, osteocalcin, and markers of bone formation

as compared to normal individuals. Half of the patients are diagnosed with osteoporosis [19]. The study of orthopedic pathology is essential for NF-1 patients due to the need to systematize data on the prevalence of skeletal anomalies in patients from different regions and identify shortcomings in the medical care in order to correct them.

The **objective** was to determine the frequency of orthopedic pathology and clinical manifestations of the disease in NF-1 patients seen in the Republic of Bashkortostan and make international comparisons.

MATERIAL AND METHODS

An orthopedic pathology was evaluated in patients from the Republic of Bashkortostan (RB), registered with an established diagnosis of "neurofibromatosis type I" with a geneticist at the Republican Medical Genetic Center. A total of 543 NF-1 patients from 433 families from the RB were examined including 259 (48 %) male and 284 (52 %) female patients aged 1 to 85 years with the mean of 30 years and 7 months. MRI and CT were performed for 60 patients and 28 patients, respectively; radiography and densitometry findings were not presented in the outpatient records. Of all the patients, four NF-1 patients received treatment with a mitogen-activated protein kinase inhibitor (selumetinib or coselugo). The examination were conducted in compliance with biomedical ethics and Good Clinical Practice (GCP). Specific clinical manifestations of NF-1 were examined in patients from the RB, the findings were compared with global data, and the frequency of occurrence and severity of tumor in patients with skeletal anomalies were compared with the general group of NF-1 patients from the RB.

Statistical processing was performed to obtain high-quality binary data using an interactive 2×2 contingency table with the calculation of association statistics (Pearson χ^2 criterion) with the Yates correction for continuity developed by Leonov (http://www.biometrica.tomsk.ru/freq2.htm), and an analysis of four-field contingency tables on the website https://medstatistic.ru/calculators/calchi.html. In addition to statistical analysis, a molecular genetic examination of DNA samples from patients was performed that resulted in mutations in the *NF1* gene identified in 20 samples. Of the 544 NF-1 patients, eight were thoroughly examined by an ophthalmologist using a slit lamp to detect iris hamartomas.

RESULTS AND DISCUSSION

NF-1 was diagnosed in 543 patients from 433 families in the RB. Taking into account the population of the republic, the prevalence of the condition was 1:7,407 people, which is more than twice the global rate (1 in 3,164 [2]). Of the 543 patients, 245 (45 %) were found to have inherited the disease from one of the parents, while 299 (55 %) were sporadic cases without a family history, which is consistent with the data of other researchers [3]. The male to female ratio was approximately 1:1.

Pigment spots were identified in 100 % of NF-1 patients and the criterion was the main one for makingthe diagnosis. Identical skin spots similar to those seen in NF-1 can occur in other hereditary tumor syndromes including tuberous sclerosis [20], Leopard [21], Noonan and Costello [22], Cowden [23], Peutz-Jeghers [24], Legius [25] syndromes, and neurofibromatosis type II [22]. Therefore, at least two criteria established by the NIH [6] are used to diagnose NF-1. Only 314 patients (58 %) out of 543 were found to have cutaneous or subcutaneous neurofibromas, which is significantly lower than the global average (99 %) [6].

No data were found on malignant MPNST tumors in NF-1 patients from the RB, which occur in 13 % of NF-1 patients [10]. Cognitive deficit was detected in 79 patients from the Republic of Bashkortostan (14.5 %), which is also significantly lower than the results of other researchers (40 %) [3]. Brain

damage was detected in some patients from the RB causing epilepsy in 20 (3.7 %) NF-1 patients, hydrocephalus in 23 (4.23 %), brain tumors in 21 (3.86 %) and brain cysts in 28 (5.15 %), which is statistically insignificantly different from the data of other researchers [8, 9, 26]. Optic nerve gliomas (34; 6.25 %), plexiform neurofibromas (38; 7 %) and Lisch nodules (5; 1 %) were not common for NF-1 patients from the RB compared to global studies [6, 8].

Plexiform neurofibromas can be detected both by visual examination and with MRI and CT [27]. They are characterized by unclear borders and invasion into surrounding tissues with location along nerve trunks, growth around deformed nerve bundles, along adjacent nerve branches, muscles and skin [28]. Based on these criteria, clinicians can establish plexiform neurofibromas in patients. Plexiform neurofibromas have a high rate of malignant transformation into MPNST tumors. Scintigraphy (with gallium-67) is recommended as a screening method for NF-1 patients with large plexiform neurofibromas. Plexiform neurofibromas have a high incidence of developing into malignant peripheral nerve sheath tumors (MPNSTs) with a 5-year survival rate of only 30 %. Fluorine-18 labeled tryptophan positron emission tomography is recommended for the differential diagnosis. Therefore, the accurate diagnosis and differentiation of MPNSTs from benign plexiform neurofibromas are critical to patient management [29].

The presence of plexiform neurofibromas is an indication for the administration of selumetinib. Cutaneous neurofibromas can be treated surgically [30] but excision of plexiform neurofibromas is difficult due to the infiltrative growth and invasion of the surrounding tissues. The use of selumetinib in different countries has shown efficacy in reducing the size of plexiform neurofibromas in children (objective response rate of 64 % [31], 68 % [32, 33]) and in adults (objective response rate of 63.6 % [34]). The efficacy of selumetinib in relation to the growth of spinal neurofibromas has also been determined [35].

MSS pathologies were detected in 206 (38 %) NF-1 patients from the RB including scoliosis detected in 95 individuals (17.4 %), short stature in 75 (13.8 %), facial dysmorphism in 49 (9 %), chest deformity in 29 (5.3 %), pseudoarthrosis of the tibia in 15 (3 %), flat feet in 10 (1.8 %), macrocephaly in 5 (1 %). Facial asymmetry, dysplasia of the sphenoid bone wing and osteoporosis were not described in any of the NF-1 patients from the RB.

A comparative analysis of impaired MSS in NF-1 patients from the RB (Table 1) indicates skeletal anomalies in general, facial dysmorphism and macrocephaly as a statistically rare condition [14–16]. There are no data on the presence of osteoporosis, facial asymmetry and dysplasia of the sphenoid bone wing, which significantly differs from the data worldwide [15, 19]. The incidence of chest wall deformities is relatively higher, and scoliosis, short stature and pseudoarthrosis are lower than the findings of other researchers, but statistically insignificant. In addition to MSS impairment NF-1 patients from the RB have a significantly lower incidence of cutaneous and subcutaneous neurofibromas, Lisch nodules, plexiform neurofibromas, and optic nerve gliomas compared to data from around the world [3, 6, 8, 10, 12] suggesting an insufficient examination of patients. Comparison of the frequency of these symptoms in individuals with impaired MSS in NF-1 patients from the RB and with data from around the world and with all NF-1 patients from the RB can be interesting.

A comparative analysis of the prevalence of clinical manifestations characteristic of NF-1 (Table 2) in NF-1 patients with orthopedic pathology from the RB, compared with global data, indicates a statistically significantly rarer registration of cutaneous and subcutaneous neurofibromas, MPNST, plexiform neurofibromas, optic nerve gliomas and learning difficulties. Compared with the general group of NF-1 patients in the RB, patients with orthopedic pathology showed a statistically insignificantly higher incidence of cognitive deficit (Table 3), but the prevalence of other manifestations was similar.

Table 1

Comparative characteristics of orthopedic pathology in NF-1

Clinical manifestations	Prevalence of the condition in the RB		Prevalence worldwide		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	%	[publication]	
skeletal anomalies in general	206	38.0	60	[14]	$\chi^2 = 9.684$; $p = 0.002$
chest deformity	29	5.3	3.7	[17]	$\chi^2 = 0.116$; $p = 0.734$
scoliosis	95	17.4	26.6	[11]	$\chi^2 = 2.914$; $p = 0.088$
low stature	75	13.8	24.0	[12]	$\chi^2 = 3.25$; $p = 0.072$
pseudarthrosis	15	3.0	5.0	[6]	$\chi^2 = 0.521$; $p = 0.471$
osteoporosis	0	0	50.0	[19]	$\chi^2 = 66.667$; $p < 0.001$
facial dysmorphism	49	9.0	53.0	[16]	$\chi^2 = 39.841$; $p < 0.001$
macrocephaly	5	1.0	25.0	[15]	$\chi^2 = 15.686$; $p < 0.001$
facial asymmetry	0	0	1.0	[15]	$\chi^2 = 10.526$; $p = 0.002$
sphenoid wing dysplasia	0	0	9.0	[15]	$\chi^2 = 9.424$; $p = 0.003$

Table 2

Comparative analysis of clinical manifestations of NF-1 in patients with orthopedic pathology

Clinical manifestations	Prevalence of the condition in NF-1 patients from the RB, *n* = 206		Prevalence of the condition in NF-1 patients worldwide		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	%	[publication]	
neurofibromas	123	59.7	99	[6]	$\chi^2 = 46.664$; $p < 0.001$
MPNST	0	0	13	[10]	$\chi^2 = 13.904$; $p < 0.001$
Lisch nodules	3	1.5	70	[6]	$\chi^2 = 100.347$; $p < 0.001$
plexiform neurofibromas	15	7.3	50	[6]	$\chi^2 = 45.369$; $p < 0.001$
optic nerve gliomas	17	8.3	27	[8]	$\chi^2 = 12.502$; $p < 0.001$
brain tumor	9	4.4	10	[8]	$\chi^2 = 2.765$; $p = 0.097$
brain cysts	13	6.3	2	[26]	$\chi^2 = 2.083$; $p = 0.149$
hydrocephalus	13	6.3	7.7	[8]	$\chi^2 = 0.307$; $p = 0.58$
epilepsy	8	3.9	8.1	[9]	$\chi^2 = 1.418$; $p = 0.234$
learning difficulties	45	22.0	40	[3]	$\chi^2 = 7.574$; $p = 0.006$

Table 3

Comparative analysis of clinical manifestations of NF-1 in patients with orthopedic pathology with a general group of patients with NF-1 from the RB

Clinical manifestations	Prevalence of the condition in NF-1 patients from the RB, *n* = 206		Prevalence of the condition in all NF-1 patients, *n* = 544		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	abs.	%	
neurofibromas	123	59.7	314	58	$\chi^2 = 0.243$; $p = 0.623$
MPNST	0	0	0	0	n/a
Lisch nodules	3	1.5	5	1	$\chi^2 = 0.409$; $p = 0.523$
plexiform neurofibromas	15	7.3	38	7	$\chi^2 = 0.02$; $p = 0.888$
optic nerve gliomas	17	8.3	34	6.25	$\chi^2 = 0.945$; $p = 0.331$
brain tumor	9	4.4	21	3.86	$\chi^2 = 0.101$; $p = 0.752$
brain cysts	13	6.3	28	5.15	$\chi^2 = 0.391$; $p = 0.532$
hydrocephalus	13	6.3	23	4.23	$\chi^2 = 1.418$; $p = 0.234$
epilepsy	8	3.9	20	3.7	$\chi^2 = 0.018$; $p = 0.894$
learning difficulties	45	22.0	79	14.5	$\chi^2 = 6.559$; $p = 0.011$

The absence of data on osteoporosis, facial asymmetry and sphenoid wing dysplasia, characteristic of NF-1 patients, among the group analyzed indicates the need for a more thorough examination of patients with mandatory consultations with an orthopedic surgeon and instrumentation researches to be performed.

CONCLUSION

Clinical manifestations of orthopedic pathology reviewed in NF-1 patients from the Republic of Bashkortostan showed a prevelance of chest deformity, scoliosis, short stature and pseudoarthrosis comparable with world data. However, skeletal anomalies in general, facial dysmorphism, and macrocephaly were not common for NF-1 patients from the RB. No data on osteoporosis, facial asymmetry and sphenoid wing dysplasia, characteristic of NF-1 patients, were found among the group examined. NF-1 patients with orthopedic pathology were found to have more frequent learning difficulties compared to the entire group of NF-1 patients from the Republic of Bashkortostan.

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