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Guidelines and recommendations

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Recommendations of the Polish Sarcoma Group on diagnostic-therapeutic procedures and control in patients with type 1 neurofibromatosis (NF1) and the associated malignant neoplasm of peripheral nerve sheaths

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Type 1 neurofibromatosis (NF1 syndrome in von Recklinghausen's disease) is inherited as an autosomal dominant disease, caused by mutations in the NF1 gene encoding the neurofibromin protein. NF1 patients are at an increased risk of the development of a malignant neoplasm and their life span is shorter by 20 years than that of the general population. National Institute of Health (NIH) criteria make a diagnosis possible from about 4 years of age. Examination of children and adults should encompass a physical and a subjective component, but also next-generation sequencing (NGS) genetic analysis, histopathological

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examination of skin lesions, neurological, ophthalmological and radiological examination. If a malignant peripheral nerve sheath tumor (MNPST) is diagnosed in a patient with NF1, the therapeutic procedure should not differ from the general principles of treating soft tissue sarcomas. Patients from the high risk group should be monitored at least once a year, the remaining patients once every 2–3 years by a specialized medical team, and every year by their primary physicians, internal medicine specialists and dermatologists. Patients should have access to genetic counselling.

Key words: neurofibromatosis 1, diagnosis, sarcomas

Aim

The guidelines contain recommendations concerning the diagnosis, treatment and control of type 1 neurofibromatosis (NF1) and of malignant peripheral nerve sheath tumor (MPNST) associated with NF1. Their aim is to help all persons who can affect decisions made in patient care, including physicians, nurses and pharmacists.

The recommendations contained in the guidelines concern the vast majority of patients in a defined clinical situation. At the same time – taking into consideration particular populations and the individual clinical situation of the patients – the document presents a number of diagnostic-therapeutic options, which allow the clinicians to select the best method of proceeding for each patient. The guidelines present interventions which may be chosen on the basis of efficacy and safety in comparison with other medical technologies and are financed in the Polish medical healthcare system. Moreover, they contain an analysis of the efficacy of alternative treatment options (including non-refunded ones). The guidelines and recommendations – on the basis of the best available evidence – have been elaborated by a multidisciplinary expert group.

Methods

The group which prepared the guidelines

The group elaborating the guidelines was made up of the panel chairman and of experts representing all specializations involved in diagnosis and treatment of soft tissue sarcomas in children and adults.

The chairman of the panel on neurofibromatosis guidelines ensured supervision of the activities related to preparation of the text and the inclusion and participation of relevant clinical experts. He moreover supervised the process of joint decision taking and ensured that each member of the panel having a significant conflict of interest would be excluded from taking part in discussions concerning the area of the conflict.

Members of the panel (tab. I) represented their specializations in all reviews and meetings. In order to ensure a multidisciplinary representation, the panel for neurofibromatosis guidelines was made up of representatives of all basic medical specializations, that is clinical oncology, pediatric oncology and hematology, radiotherapy, oncological surgery, molecular diagnostics, radiology, pathomorphology, nuclear medicine and physical therapy.

Table I. Members of the panel elaborating the recommendation including their specializations and the scope of their work

Author	Specialization	Scope of work
Piotr Rutkowski	general and oncological surgery	guideline scope, literature search, guideline approval, evaluation of the quality and strength of the recommendations, approval of final version
Anna Raciborska	• hematology and pediatric oncology • pediatrics	approval of recommendations concerning pediatric patients, participation in preparation of chapters concerning pediatric patients, analysis of the literature concerning pediatric patients, correction of the manuscript
Anna Szumera-Ciećkiewicz	pathology	preparation of text concerning histopathological diagnosis, analysis of the literature concerning histopathological diagnosis, preparation of histopathological photographs, correction of the manuscript
Paweł Sobczuk	clinical oncology	preparation of text on MPNST treatment, editing the reference list
Mateusz Spałek	radiation oncology	preparation of text on MPNST treatment
Hanna Koseła-Paterczyk	clinical oncology	preparation of an outline of the guidelines during consensus meetings
Iwona Ługowska	clinical oncology	preparation of an outline of the guidelines during consensus meetings
Katarzyna Bilska	• medical rehabilitation • pediatrics	participation in preparation of chapters concerning the pediatric population, participation in preparation of the reference list

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Table I. cd. Members of the panel elaborating the recommendation including their specializations and the scope of their work

Author	Specialization	Scope of work
Monika Gos	laboratory medical genetics	participation in preparation of chapters concerning molecular diagnosis, participation in preparation of the reference list
Janusz Ryś	pathology	participation in preparation of the text concerning histopathological diagnosis
Ewa Chmielik	pathology	participation in preparation of the text concerning histopathological diagnosis
Andrzej Tysarowski	molecular biology	participation in preparation of the text concerning molecular diagnosis
Konrad Zaborowski	general surgery	participation in preparation of the text concerning surgical treatment
Małgorzata Oczko-Wojciechowska	pathomorphology	preparation of an outline of the guidelines during consensus meetings
Patrycja Castaneda-Wysocka	radiology	preparation of text on radiological diagnosis
Donata Makuła	radiology	preparation of an outline of the guidelines during consensus meetings
Marcin Zdzienicki	general, oncological and vascular surgery	preparation of an outline of the guidelines during consensus meetings
Marcin Ziętek	general and oncological surgery	preparation of an outline of the guidelines during consensus meetings
Piotr Fonrobert	patient association	preparation of an outline of the guidelines during consensus meetings
Kamil Dolecki	patient association	preparation of an outline of the guidelines during consensus meetings
Marek Dedecjus	nuclear medicicine	preparation of text on PET analysis
Anna M. Czarnecka	• clinical oncology • molecular biology	literature analysis, participation in elaborating the basis of the guidelines, participation in preparation of chapters concerning molecular diagnosis, pediatric patient and oncology, participation in preparation of reference list, editing and correction of the manuscript, approval of final version

Search for evidence and formulating the recommendations

In order to find significant scientific evidence, non-systematic searches were performed on clinical practice guidelines and databases of medical information. The search for clinical practice guidelines encompassed recommendations of diagnostic-therapeutic procedures in soft tissue sarcomas /type 1 neurofibromatosis published in Polish and English during the last 5 years. The quality of the found guidelines was evaluated using the AGREE II tool. A non-systematic search was also performed on medical information databases (PubMed) in order to obtain crucial literature. Papers from additional sources considered as important for the guidelines could be included in the process of literature review. In particular, a review was made of all phase II and III clinical trials available in PubMed, published in the years 1990–2021 and containing the word neurofibromatosis 1 and MPNST and current ESMO, ASCO, NCCN and PTOK recommendations

Recommendations contained in the guidelines are based on a critical evaluation of the evidence combined with clinical knowledge and consensus of a multidisciplinary expert panel. They were agreed upon by members of the panel after a review and discussion of clinical evidence and a discussion of their interpretation. Decisions concerning the inclusion of the found evidence into the created guidelines were made on the basis of an informal consensus.

Quality of the evidence and strength of the recommendations

Randomized controlled trials (RCT) are considered to be the basis of high quality clinical evidence. However, much of the available evidence is based on data from trials without randomization or on retrospective or prospective observational trials. In many clinical situations there are no significant clinical data and the procedure is based on clinical experience.

For this purpose the classification of recommendations was based both on the available clinical evidence as well as the consensus of the panel reached during an informal process. The level of the evidence depends on the following factors, which were taken into consideration during the discussion process: quality, quantity and data integrity (tab. II, III).

The participation of the chairman and the members (authors) of the panel was voluntary and they did not receive remuneration for their engagement in the process of guideline elaboration. All authors were asked to divulge information on potential conflicts of interest. Each author presented a DOI declaration even if there were no areas of conflict. Each author was responsible for ensuring that their DOI declaration was precise and truthful. Each member of the panel who had a significant conflict of interests was excluded from participation in discussions and voting concerning the area of conflict.

Table II. Quality of the evidence

Grade	Definition
I	evidence from at least one large randomized clinical trial (RCT) with a high methodological quality (low risk of a systematic error) or metaanalyses of properly planned RCT without heterogeneity
II	small RCT or large RCT with the risk of a systematic error (lower quality of the methodology) or metaanalysis of such trials, or of RCT with demonstrated heterogeneity
III	prospective cohort trials
IV	retrospective cohort trials or clinical-control trials
V	trials without control group, case descriptions, expert opinions

Source: ESMO Guidelines Committee (2020); Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores; accesss on 16.07.2021

Table III. Strength of the recommendations

Category	Definition
category 1	recommendation based on high quality evidence, with a unanimous approval or high degree of consensus from the expert panel
category 2A	recommendation based on lower quality evidence, with a unanimous approval or high degree of consensus from the expert panel
category 2B	recommendation based on lower quality evidence, in respect to which the expert panel attained a moderate level of consensus

Source: AOTMiT elaboration on the basis of The National Comprehensive Cancer Network. Development and Update of the NCCN Guidelines®, access on 16.07.2021

According to the authors, this elaboration contains the most justified principles of diagnostic-therapeutic procedures. They should, however, be interpreted in relation to the particular clinical situation. The recommendations do not always correspond to the current bases of refunding treatment in force in Poland (which is noted in the text). In the case of doubt, the current possibilities of refunding particular procedures should be ascertained.

Introduction

Type 1 neurofibromatosis (NF1 syndrome, von Recklinghausen disease) is a disease unit with the symbol OMIM 613113 in the catalogue of genetic diseases *Online Mendelian Inheritance in Man* (the so-called McKusick catalogue). NF1 is an inborn syndrome of skin and neurological diseases (facomatoses), observed regardless of the ethic group, race and sex with a frequency of 1:2500–3000 births [1, 2]. The disease is inherited in an autosomal dominant way and is caused by mutations in the *NF1* gene located on the long arm of chromosome 17 encoding the neurofibromin protein. Children of patients with an NF1 diagnosis have a 50% risk of inheriting the disease. However, one-half of NF1 cases are due to new mutations and are not familial (II) [3]. *De novo* mutations occur mainly in paternal chromosomes [4]. Patients with NF1 have an increased risk of developing malignant neoplasms and their life spans are about 10–20 years shorter than in the general population [5, 6]. The most recent analysis of the whole population of France indicated that an NF1 diagnosis has a much stronger effect on the expected life span in women than in men – 16.5 years for men and 26.1 years for women [7, 8]. Similar results have been published by Italians, who observed an average shortening of the lifespan of NF1 patients by 20 years [5]. Analysis of death certificates in the United States indicated that persons with NF1 lived for 54.4 years on the average and the median was 59 years – considerably below population norms which were respectively 70.1 and 74 years for the same period [6].

From the point of view of oncology it is important that the *NF1* gene is a tumor suppressor in cells [3]. Neurofibromin is a member of a family of proteins which activate guanosine triphosphate hydrolase (GTPases) (guanine nucleotide activating protein – GAP), which stimulate endogenous GTPase activity in the RAS (rat sarcoma virus protein*)* protein family – p21. A key role of neurofibromin is decreasing the level of activated RAS bound to GTP through stimulation of low endogenous GTPase activity of the RAS proteins themselves, thus promoting the conversion of active RAS-GTP to its inactive state RAS-GDP [9]. RAS activates a number of signal pathways which include the signal pathway of stem cell factor (SCF)/c-kit, mammalian target of rapamycin (mTOR) and mitogen-activated protein kinases (MAPK) [10].

Detecting the *NF1* mutation does not allow prediction of the intensity or complications of the disease. No direct genotype-phenotype correlations have been identified for patients with *NF1* mutations [7]. In patients with mutations of this gene, optic nerve gliomas may occur, or gliomas of the central nervous system, sarcomas of the malignant peripheral nerve sheath tumor (MPNST) type and other more rare neoplasms (among others gastrointestinal stromal tumors – GIST). In agreement with the role of the *NF1* gene as a classical tumor suppressor, in some neoplasms of NF1 patients loss of heterozygosity (LOH) or somatic mutations have been detected in the second initially normal allele of the gene [3]. The frequency of occurrence of somatic *NF1* mutations in the cells of selected neoplasms is [11, 12]:

- acute myelocytic leukemia (AML) 3.5–23.6%
- desmoplastic melanoma 45–90%
- skin melanoma 12–30%
- gliomas 14–23%
- colorectal adenocarcinoma 3.8–6.25%
- neuroblastoma 2.2–6%
- acute T-cell lymphoblastic anemia 3%
- paraganglioma / phaeochromocytoma 21–26%
- ovarian cancer 12–34.4%
- lung adenocarcinoma 7–11.8%
- breast cancer 2.5–27.7%
- squamous cell carcinoma of the lung 1.3–11%
- transitional cell carcinoma of the bladder 6–14%

Clinical diagnosis of type 1 neurofibromatosis

The general principles of NF1 diagnosis are similar in all age groups. Differences in the diagnosis criteria concern the size of the *café au lait* (CAL) spots – in small children 0.5 cm spots can already be classified as a disease symptom (in adults the minimum is 1.5 cm) [13]. Defined diagnostic criteria did not exist until 1987, when they were elaborated and presented by the National Institute of Health (NIH) in the USA during the NIH Consensus Development Conference – NIH-CC-86 with later modifications [14]. These criteria were maintained in successive guidelines for neurofibromatosis treatment [1]. NIH guidelines state that to diagnose the disease at least 2 of the symptoms mentioned below have to be present:

- at least 6 *café au lait* spots with a diameter of 0.5 cm or larger before puberty and 1.5 cm or larger after this period
- 2 or more neurofibromas or 1 plexiform neurofibroma,
- freckles on areas of the body not accessible to light (armpits, groin, area of pubic mound) – Crowe symptom,
- optic nerve glioma(s)
- 2 or more Lisch nodules (iris hamartoma),
- characteristic bone symptoms (sphenoid bone dysplasia and/or thinning of the core layer or long bone dysplasia with or without formation of pseudoarthrosis),
- 1st degree relative (parents, siblings, children) fulfilling the above criteria.

The criteria defined by NIH make it possible to diagnose the disease at about 4 years of age, whereas fully symptomatic disease generally develops up to the age of reaching sexual maturity; 97% patients with NF1 fulfill NIH criteria at the age of 8 years, and all at the age of 20 years [15]. Characteristic bone lesions generally appear within the first year, and the average age of diagnosing an optic nerve glioma varies between 3 to 6 years [7]. In clinical practice NF1 can be suspected with a high probability in babies with *café au lait* type spots who have an affected parent; in babies in whom specific bone dysplasias are diagnosed, or plexiform neurofibroma; in children up to 2 years of age in whom >6 *café au lait* spots were observed; and in children up to 3 years of age, in whom >10 such *café au lait* spots were detected [16, 17].

A pathognomic symptom for NF1 are also FASI, or focal areas of increased signal intensity in the T_2 sequence in MRI, described also in practice as UBO, or unidentified bright objects. For this reason an NF1 diagnosis may also be made in patients with many *café au lait* spots, for whom MRI of the central nervous system has been shown to have FASI. The first MRI analysis is in general performed in children aged 3 to 4 years, as for such small patients it requires general anesthesia [16, 17].

The fulfilling by the patient of the above-mentioned NIH criteria is associated with a high probability of identifying a mutation in the *NF1* gene. The mutation in the *NF1* gene is detected in 97% of fully symptomatic patients, if all available diagnostic methods, including NGS, are used together [18]. If the genetic analysis is performed in patients only fulfilling NIH criteria, mutations are detected in 78–95% depending on the used method of diagnosis and sequencing. In recent years a revision of the NIH criteria has been recommended in order to take into consideration the availability of molecular analyses in respect to pathogenic NF1 variants and also clinical characteristics (e.g. choroid abnormalities, *nevus anemicus*), which often occur in childhood, but were unknown during the NIH Consensus Conference [19, 20]. Currently NIH criteria are also considered insufficient for diagnosing babies. Over 50% of children under the age of 2 years with sporadic NF1 fulfill only one NIH criterium, which often leads to delayed diagnosis. Juvenile xanthogranuloma (JXG) and *nevus anemicus* occur in most children under the age of 2 years with NF1 and have been observed in 80% of patients not fulfilling the NIH criteria [7].

The new diagnostic consensus elaborated in 2021 [21] encompasses the following criteria:

A.

Diagnostic criteria for NF1 are fulfilled in a person whose parent has not been diagnosed with NF1 if 2 or more of the properties listed below are present:

- 6 or more *café au lait* spots with the largest diameter over 5 mm in persons before puberty and over 15 mm in persons after puberty,
- freckles in the armpit or groin area,
- 2 or more neurofibromas of any type or 1 plexiform neurofibroma,
- optic pathway glioma,
- at least two 2 Lisch iris nodules identified by a slit lamp examination or at least 2 choroid abnormalities (CA) – defined as light, heterogeneous nodules visualized by optical coherent tomography (OCT) / near infrared reflection (NIR),
- characteristic bone lesions, such as of the sphenoid bone such as anterior-lateral flexion of the tibial bone or pseudoarthrosis of long bones,
- heterozygous pathogenic variant in the *NF1* gene with the allele fraction at least 50% in an apparently normal tissue such as leukocytes.

B.

Child of a parent who fulfills diagnostic criteria defined in A should be diagnosed with NF1, if one or more criteria from A are present.

Large NF1 symptoms include:

- *café au lait* spots (occur in >99% of affected persons),
- freckles and hyperpigmentation (70%),
- peripheral fibromas (>95%),
- Lisch nodules, that is iris hamartoma nodules, not affecting vision (>90%).

Small symptoms include:

- macrocephaly (45%),
- short stature (30%).

Moreover, in patients with NF1 secondary symptoms and complications may occur, including mental retardation (30%), epilepsy (5%), plexiform neurofibromas, which may undergo malignant transformation (35%). Orthopedic complications (25%) in the form of bone dysplasias and deformations in general manifest as chest scoliosis. The stenosis of renal vessels is rare (1.5%), but may lead to the development of arterial hypertension (nephrogenic). Tumors of the central nervous system, most commonly optic nerve gliomas, occur only in several percent of the patients, but develop already in children [7]. In children, similarly as in adults, clinical manifestations vary. The first symptoms may occur at birth or may appear as the child grows (tab. IV) [1, 13].

The diagnosis is generally based on clinical characteristics observed in a physical examination and in the medical history. Differential diagnosis should include other syndromes with perturbed pigmentation, such as the McCune-Albright, segmental NF, type 2 NF and Watson syndrome or schwannomatosis [22].

To make a diagnosis, examination of children and adults should include:

- physical examination and medical history (II, 1),
- NGS analysis of the *NF1* gene or sequencing of a panel of genes/exome,
- histopathological analysis of skin/subcutaneous tissue lesions,
- neurological examination,
- ophthalmological examination,
- radiological examination (computed tomography, magnetic resonance).

In the physical examination attention should be paid to skin lesions (*café au lait* spots, freckles in groin and armpits, neurofibromas – including plexiform, other pigmentation perturbations), ophthalmological, skeletal and neurological changes and the arterial blood pressure should be measured [23]. In imaging studies characteristic changes are often detected in the central nervous system, hyperintense foci in T_2 dependent images and the FLAR sequence in deep white matter, basal nuclei and the corpus callosum. Lesions of the lambdoid suture, meningeal calcification of the cranial vault or the *moya-moya* phenomenon are rarely detected in NF1 [24].

Table IV. Age at which particular symptoms appear during the course of type and NF

Clinical symptoms	Frequency (%)	Age of symptom appearance
café au lait spots	99	from birth to 12 years
freckles in groin and armpits	85	from 3 years to puberty
lisch nodules	90–95	from 3 years
skin neurofibromas	99	from 7 years, more common during puberty
plexiform neurofibromas	in 30% visible upon clinical examination, in 50% observed in imaging studies	from birth
disfiguring facial plexiform neurofibroma	3–5	from birth to 5 years
MPNST	2–5	from 5 to 75 years
scoliosis	10	from birth
scoliosis requiring surgery	5	from birth to 18 years
Pseudoarthrosis of the tibial bone	2	from birth to 3 years
renal artery stenosis	2	whole life
phaeochromocytoma	2	over 10 years
serious impairment of cognitive functions (IQ 70)	4–8	from birth
problems with learning	30–60	from birth
epilepsy	6–7	whole life
optic nerve glioma	15 (only 5% symptomatic)	from birth to 7 years
brain glioma	2–3	whole life
dysplasia of sphenoid bone	1	inborn
cerebral aqueduct stenosis	1.5	whole life

Molecular diagnosis of type 1 neurofibromatosis

Type 1 neurofibromatosis is a genetic disease inherited in an autosomal dominant fashion. In about 95% patients fulfilling the criteria of a clinical diagnosis of NF1 elaborated by the National Institute of Health a pathogenic variant is identified in one copy of the *NF1* gene [1]. In most cases (appr. 90%) point mutations (changes in nucleotide sequence) are found in patients. The most common mutations cause a loss of function of the protein encoded by the *NF1* gene, that is:

- mutations causing a premature STOP codon (the so-called nonsense mutations),
- insertion/deletion mutations causing a change in the reading frame,
- mutations perturbing transcript splicing (the so-called splicing mutations).

In about 5–7% patients large deletions are identified which encompass single exons, a fragment of the *NF1* gene or the whole gene. In rare cases chromosomal aberrations are detected, e.g. translocations which can affect gene expression. In about 2% of patients fulfilling NIH criteria, mutations in the *SPRED1* gene are found, however, it should be stressed that the phenotype of these patients described as Legius syndrome differs from a typical form of NF1 by the absence of neurofibromas and Lisch nodules. In single patients with spinal neurofibromas mutations in the *PTPN11* gene have been detected [2].

Molecular analysis in the case of a suspicion of type 1 NF is a supplementary procedure [25]. The disease is predominantly diagnosed on the basis of clinical criteria [22]. The clinical experience of the authors and analysis of the literature indicates that molecular analysis may be useful in the following situations [1, 18]:

- clinically doubtful cases in which single clinical symptoms occur and it is not possible to make an unequivocal diagnosis on the basis of the patient's phenotype by itself,
- family members of patients with an NF1 diagnosis, in whom clinical symptoms of NF1 have not yet occurred,
- cases in which it is necessary to make a clinical differentiation between NF1 and Legius syndrome or a RASopathy, and the clinical picture is not unequivocal for any of the clinical entities.

In the remaining cases molecular analysis has a supplementary character. The result of a molecular analysis by itself is not a confirmation of an NF1 diagnosis as clinical characteristics which indicate the possibility of the disease have to be present [13, 22].

Outline of molecular diagnosis of NF1

Because of the high percentage of point mutations in patients with the *NF1* mutation and the possibility of mutations in other genes, the optimal diagnostic technique in the case of suspected type 1 NF is targeted (panel) next generation sequencing (NGS). Because of the character of the analysis it is always necessary to obtain an informed consent declaration for the genetic analysis. The analysis is performed on material from saliva or venous blood (at least 4 ml in older children and adults and 2 ml in babies) taken on EDTA (morphological test tube). For analysis by the NGS technique, genomic DNA isolated from nucleated cells of the patient (e.g. lymphocytes) is used. This technique requires a minimum of 3µg of DNA with O.D. 260:280 nm ≥1.8. The presence of the detected variants is confirmed by Sanger sequencing. If bioinformatic analysis performed for data obtained by the NGS technique indicates the presence of quantitative changes in the DNA encompassing at least one exon, this always requires confirmation by other methods, such as qPCR or MLPA (multiplex ligation-dependent probe amplification), which is described below [26, 27].

A serious challenge for clinicians and geneticists working with NF1 is the identification and characterization of *NF1* mutations in individual patients. This problem is due to many properties of the *NF1* gene itself, including its large size (~350 kbp) and complex structure (61 exons), lack of repeated localization of mutations (so-called hot spots), and thus a broad spectrum of reported mutations. The *NF1* gene encodes neurofibromin and is localized in the 17q11.2. locus and encompasses over 350 thousand base pairs. According to the NM_001042492.3 transcript, which is currently considered to be canonical, it contains 58 exons and is transcribed to an mRNA of about 12 kb, containing an 8520 nucleotide open reading frame. Neurofibromin is a multidomain protein of 2839 amino acids. Currently in the Human Gene Mutation Database Professional 2021.2 (HGMD®, access on 10.09.2021; http://www.hgmd.cf.ac.uk/ac/index.php) over 3804 different heritable mutations in *NF1* have been reported as the cause of type 1 neurofibromatosis. The spectrum of *NF1* mutations is thus well defined and encompasses missense/nonsense mutations– appr. 32.7%, splicing mutations – 15%, small deletions – 26.1%, small insertions/duplications – 10.5%, changes of the deletion/insertion type – 2.1%, extensive deletions >20 bp – 11.2%, large insertions >20 bp – 1.5%, complex rearrangements – 0.39% and 4 putative regulatory mutations. There is no evidence of any localized, reproducible mutation clusters within the *NF1* gene. Most (>80%) of constitutive *NF1* mutations are mutations causing loss of function – their presence causes almost complete absence of the transcript or loss of function of the protein [9, 28, 29].

To classify variants identified in the *NF1* gene, a system elaborated by the American College of Medical Genetics is used [30]. Identification of a pathogenic or potentially pathogenic variant in one copy of the *NF1* gene is confirmation of a clinical diagnosis of type 1 NF. However, its absence does not confirm but also does not exclude the clinical diagnosis of the disease because of the possibility of the presence of deep intron or regulatory mutations or larger deletions, which cannot be identified by targeted sequencing. In this case another range of genetic analyses should be considered [24].

If a variant which cannot unequivocally be classified as pathogenic/potentially pathogenic or benign/potentially benign is discovered in patient, that is a variant of uncertain clinical significance, the interpretation of its pathogenicity in the context of the disease should approached with care. In this case the basic analysis which should be performed is analysis of the inheritance of the variant in the family and checking if it segregates with the disease or whether it occurs in asymptomatic parents or other members of the family. It is optimal to perform functional analyses, though this is not routinely available in diagnostic laboratories in Poland [24].

The analysis of extensive deletions/duplications in the *NF1* gene should be performed by the method of multiplex ligation-dependent probe amplification (MLPA) – a technique for analysis of the change in the copy number of DNA fragments. This makes possible the identification of the deletion of individual exons of the *NF1* gene as well as determining the extent of the deletion in the case of larger chromosome changes. Routinely in NF1 diagnosis the P081/P082-NF1 kits are used. If the whole gene is deleted, the size of the deletion can be determined using the P122-NF1 area kit (MRC-Holland) [27, 31].

In cases in which a point mutation or a deletion has been excluded, the analysis must be extended to the identification of deep intron mutations which perturb splicing of the pre-mRNA of the *NF1* gene. Such mutations may cause the deletion of a fragment of the transcript or the insertion of additional sequences, resulting in general in a change of the reading frame and the absence of the normal protein. Splicing mutations in *NF1* (deep intron mutations) are mutations resulting in the formation of new splicing acceptor/donor sires and also changes in regulatory ESE, ESS, ISS, ISE sequences or the activation of cryptic sites. This may lead to inclusion of a new exon into the transcribed mRNA and the translation to an aberrant neurofibromin protein. Deep intron mutations constitute ~2% of all described mutations in the *NF1* gene. The material for analysis in this case is RNA which is reverse transcribed into cDNA, which serves for amplification of *NF1* gene fragments which can then be sequenced using the Sanger technique or next generation sequencing. If aberrant splicing is detected, point mutations are sought in the relevant part of the *NF1* gene, as their presence is the cause of splicing perturbations [24, 32].

In the literature there are also descriptions of *NF1* mutations in a mosaic system, thus only in part of the cells. In such a situation mutations may not be detected in blood or may be present in less than 50% of the cells. If a mosaic form of NF1 is suspected, additional analysis from an affected tissue or tissues should be considered [21, 33].

For the analysis of the presence of specific mutations in members of families with NF1, generally sequencing is performed by the Sanger method. Only the sequence of a fragment of the *NF1* gene is analyzed in which in the proband the presence of a pathogenic variant/ a potentially pathogenic variant /a variant of unknown clinical significance was detected [24].

The NGS technique allows the simultaneous analysis of selected genes among which – in the case of a suspicion of NF1 – the following must be included: *NF1*, *SPRED1* and *PTPN11* (fig. 1). Their analysis should include coding sequences and sequences at the intron/exon junction (at least 10 nt, longer, if pathogenic variants located at a larger distance from the exons have been described) of the analysed genes. The analyzed panel should allow the analysis of other genes associated with the pathogenesis of diseases from the group of RASopathies, including Noonan syndrome. In the course of these diseases pigmentation perturbations may occur which accompany characteristic inborn errors and dysmorphic traits which may also be observed in some NF1 patients. It is debatable whether in the panel the *MMR* genes (*MLH1*, *MSH2*, *MSH6, PMS1* and *PMS2*) should be included, whose mutations are responsible for the constitutional mismatch repair deficiency syndrome (CMMRD) – an autosomal recessive rare disease in which in addition to higher risk for various types of neoplasms *café au lait* spots are detected. The CMMRD syndrome is estimated to be responsible for the occurrence of symptoms in 0.41% of patients with NF1 symptoms, without mutations in *NF1* and *SPRED1* genes [30, 34].

However, the authors of population studies suggest that before sequencing MMR genes a screening should be performed confirming the presence of perturbations of DNA repair systems, e.g. the analysis of minisatellite sequence instability. In differential NF1 diagnosis, depending on the clinical picture of a given patient, among others the following should be considered: Legius syndrome, Watson phenotype, Noonan syndrome, McCune-Albright syndrome, Costelo syndrome, Jaffe-Campanaci syndrome or LEOPARD syndrome [35–37].

NF1 diagnosis in oncology

Plexiform neurofibromas (PNF), which are present in 30–50% of patients with NF1, in about 10–15% of cases develop into aggressive malignant peripheral nerve sheath tumors (MPNST), which are a frequent cause of deaths [38]. In these tumors somatic mutations ensure a selective dominance of cell growth and promote the development of the tumor. NGS detects hereditary or somatic *NF1* mutations in over 90% of MPNST tumors. Diagnosis of an *NF1* mutation during evaluation of MPNST requires the preparation of a paraffin block containing a section of the neoplasm or a histopathological preparation, which enables the localization of a fragment of neoplastic tissue at least 4 mm x 4 mm x 1 mm in size containing only MPNST. The pathogenicity of the mutation should be confirmed at least on the basis of one database of pathogenic mutations, e.g. PubMed ClinVar database, LOVD (Leiden Open Variation Database – http://www.LOVD.nl/NF1), NCBI dbSNP (database of Single Nucleotide Polymorphisms, ClinVar), and in the case of changes in MPNST also on the basis of The Cancer Genome Atlas (TCGA), the database of the International Cancer

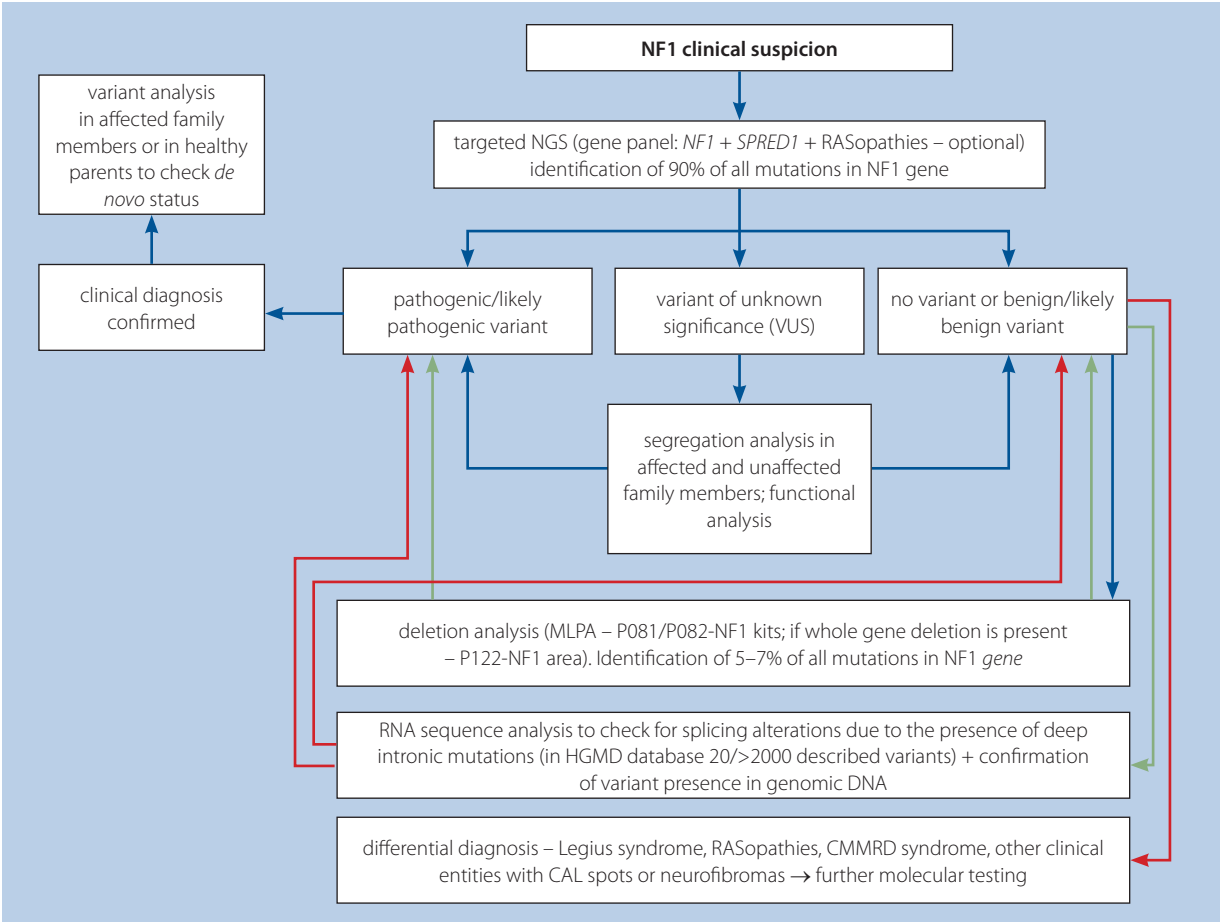

Figure 1. Proposed diagnostic procedure

Genome Consortium (ICGC) or in the Catalog of Somatic Mutations in Cancer (COSMIC – http://cancer.sanger.ac.uk/cosmic). Mutations and their putative effect at the protein level should be named according to the guidelines of the Human Genome Variation Society (https://www.hgvs.org/), and numbering of the mutations should be based on the NF1 mRNA sequence from GenBank (NM_000267.2) [31]. Analyses of somatic mutations should always be compared to germline DNA sequences as described above [1, 39].

Molecular analysis of the *NF1* gene should be performed in a medical diagnostic laboratory which specializes in medical genetic analyses, has relevant diagnostic equipment, experience in molecular techniques and appropriate certificates of quality.

Histopathological diagnosis

A key clinical manifestation of NF1 is the presence of neurofibromas, and in some patients the development of MPNST, in general from a previously present neuroma, especially of the plexiform type. Neurofibromas are benign tumors of peripheral nerve sheaths, composed of fusiform Schwann cells with hyperchromatic, wavy nuclei, often mixed with fibroblasts and collagen strands (fig. 2).

Cytological atypia in these tumors is considered to be a symptom of degeneration and as a single symptom is not troubling. Highly malignant MPNST tumors representing the other end of this histological spectrum in general show clear properties of a malignant neoplasm, including architecture typical for sarcomas, high mitotic activity and necrosis. However, diagnosis of MPNST with a low grade of malignancy is often problematic as there are no well-defined criteria. Tumors with troubling morphological properties, such as increased cell count or slightly increased mitotic activity, which do not fulfill the criteria for MPNST with a low grade of malignancy are described in the literature and diagnostic practice as atypical neurofibroma or atypical neurofibromatic neoplasm with an uncertain degree of histological malignancy [40, 41].

The usefulness of additional analyses in histopathological diagnosis (among others p16 and p53, and also Ki-67 and loss of H3K27me3) has been well described but finally is of only marginal value for differentiation.

MPNST shows loss of the *CDKN2A* gene which encodes the p16 protein leading to the loss of p16 expression. Even though most neurofibromas maintain high expression of p16, a decrease or loss may occur in atypical cases. Thus though lack of p16 staining may suggest an early stage of neoplastic

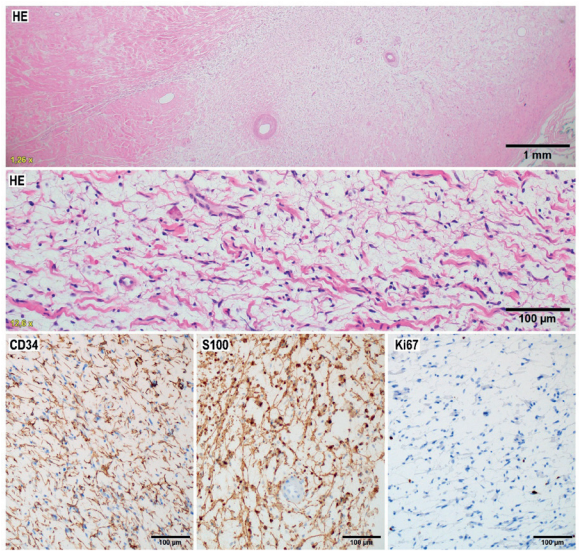

Figure 2. Classical histopathological appearance of a neurofibroma

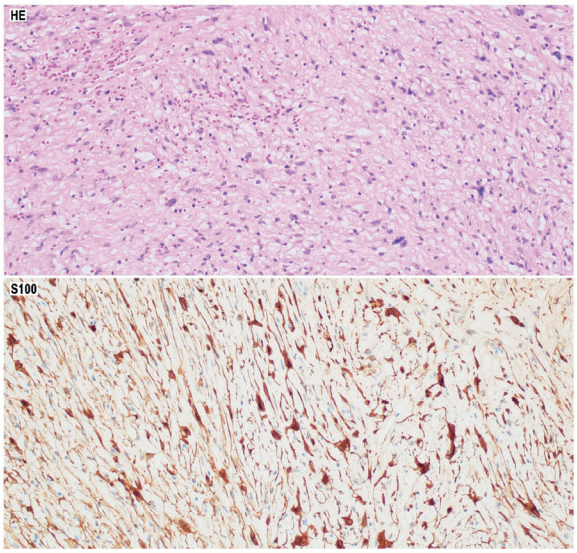

Figure 3. Neurofibroma with cytological atypia

transformation, it does not necessarily indicate malignancy. Similarly, MPNST have a tendency to show a higher p53 expression (>10% cells), but the use of this marker is limited to differentiating between atypical neurofibromas, an atypical neurofibromatic neoplasm of uncertain histological degree of malignancy and low grade MPNST as these tumors in general show a low expression of p53 (<5% cells). In the case of MPNST a higher proliferative activity can be expected (Ki-67 > 10%) in comparison to neurofibromas (Ki-67 < 5%), but there are no validated boundary values. Moreover, it has been shown that histone 3 trimethylated at the lysine 27 residue (H3K27me3) is lost in a large part of high grade MPNST, but in the tumors mentioned above this can be maintained or heterogeneous. As a consequence differentiating neurofibromas with increased cell count or slightly increased mitotic activity from low grade MPNST is based primarily on the evaluation of morphological characteristics and the pathomorphologist's experience [40–43].

In NF1 the challenge is to monitor the progression within neurofibromas, in which an inherent element is the evaluation of biopsy materials. Growing, painful lesions or the appearance of troubling properties in imaging studies (magnetic resonance and/or positron emission tomography) are indications for surgical removal or a diagnostic biopsy (optimally 4 cylinders each 2 cm long) from tumor fragments suspected of transformation on the basis of the evaluation of imaging studies [40–43].

Neurofibroma with cytological atypia or with increased cell count

Nuclear atypia occurs in some sporadic and NF1 associated neurofibromas and such neoplasms are often described as "atypical neurofibromas" (fig. 3). There are no reliable data on the frequency of occurrence – probably because there is a large variability in the use of this terminology among pathomorphologists. Initially on the basis of *CDKN2A* gene loss it was postulated that neurofibromas are lesions progressing to MPNST. However, there is no clinical evidence that cytological atypia indicates a faster malignant transformation [40].The presence of focal or even more distinct atypia in neurofibromas is not troubling when it occurs without an increase in mitotic activity in the context of classical neurofibroma architecture: randomly arranged S100- and/or SOX10-positive cells with stroma rich in collagen and a network of CD34-positive fibroblasts. This type of nuclear atypia can mean a 2–3-fold (or greater) increase in the size of the nucleus, its hyperstaining, irregular distribution of chromatin and multinuclear or "strange" forms. The state in which diffuse "strange" nuclei occur with maintained cell count without increased mitotic activity with maintained neurofibroma architecture is sometimes described as "degenerative atypia". In practice it has no clinical significance. It should be stressed that there are no scientific criteria allowing to clearly distinguish "degenerative atypia" from "true atypia" (neoplastic) which may precede a malignant transformation [40, 41].

In a cellular neurofibroma an increase in cell count is observed, which is the only troubling morphological character (without mitotic activity, cytological atypia or loss of neurofibroma architecture). The illusion of higher cell count is also noted in tumors with a massive lymphocyte-histiocytic infiltration. Similarly as in the case of with atypia alone, there are no decisive data concerning the risk of progression to MPNST. From the immunohistochemical aspect a low value of the proliferation index (Ki-67) and the small number of cells showing nuclear expression of p53 can also be considered as additional characteristics indicating the diagnosis of an atypical/cellular neurofibroma. Strong expression of the S100 (cytoplasmic and nuclear) and of SOX10 (nuclear) protein underlines the elements of Schwann cells, whereas CD34 identifies fibroblasts forming a pattern resembling a net – typical for the maintained neurofibroma architecture [40, 41].

Atypical neurofibromatic neoplasm with an uncertain degree of histological malignancy

Neurofibromatic neoplasms can be considered as showing an uncertain malignant potential when at least 2 of the characteristics mentioned below are present (tab. V) [40, 41]:

- nuclear atypia,
- increased cell count,
- variable loss of neurofibroma architecture (e.g. bundle-like growth, "herringbone", "pinwheel" and/or loss of network of CD34-positive fibroblasts),
- and/or mitotic activity outside isolated mitotic figures (>3 mitoses in 10 high power fields, <15 mitosis per 1 mm^2).

Though such tumors have sometimes been described as low grade MPNST, they were mainly associated with a low recurrence risk and essentially no risk of metastases. Qualifying these tumors as malignant could have led to excessively aggressive therapy, with the burden of an increased risk of potential undesirable side effects. Diagnosing atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) is also applicable to small biopsies in which worrying atypical properties are observed and the MPNST criteria are not fulfilled. In such cases the correlation of the clinical presentation with the microscopic and radiological picture is of particular importance, and in some cases it may be necessary to obtain another sample of the material for a histopathological examination [40, 41].

Currently there is no available immunohistochemical or genetic test defining the state of the malignancy in atypical neurofibromatic neoplasms. Besides a microscopic evaluation, the analysis of the variation or total loss of the expression of the S100 or/and SOX10 protein and the loss of the network of CD34-positive fibroblasts may be helpful. Neurofibromas and atypical neurofibromas in general have a low level of proliferative activity Ki-67 (2–5%). Focally higher indices of proliferation (Ki-67 at the level of 10%) may help in diag-

Table V. Criteria in histopathological diagnosis – spectrum of changes occurring in type 1 neurofibromatosis

Diagnosis	Definition	Mitotic activity		Necrosis	IHC
		mitoses/ mm^2	mitoses/ 10 HPF		
neurofibroma	benign neoplasm from Schwann cells with thin and wavy nuclei, delicate protrusions, myxoid to collagen stroma (thick bands of collagen)	absent	absent	absent	• strongly positive S100(+) and SOX10(+) staining • CD34(+) stroma of fibroblasts forming a "reticular network" • H3K27me3 • stain maintained
plexiform neurofibroma	neurofibroma growing and diffusion and replacing the nerve, often encompassing many nerve bundles	absent	absent	absent	EMA(+) w perinerve cells
neurofibroma with atypia/ ancient neurofibroma	neurofibroma exclusively with cellular atypia, often manifesting as "strange nuclei"	absent	absent	absent	as in neurofibroma
cellular neurofibroma	neurofibroma with increased cell count with maintained architectonic neurofibroma characteristics, without mitotic activity	absent	absent	absent	as in neurofibroma
atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP)	≥2 of 4 characteristics • cytological atypia • loss of neurofibroma architecture • increased cell count • mitoses – as above	<1.5	<3	absent	• S100(+/–) and SOX10(+/–) • loss of H3K27me3 expression • loss of positive stain (heterogeneous reaction more common)
MPNST, low-grade	ANNUBP characteristics and mitoses – as above	1.5–4.5	3–9	absent	• S100(+/–) positive <50% • SOX10(+/–) positive <70% • GFAP(–/+) positive 20–30% • H3K27me3# • loss of positive reaction • epitheliod MPNST: maintained strong expression of S100; SOX10; H3K27me3#; loss of expression of SMARCB1/INI1
MPNST, high-grade	ANNUBP characteristics and mitoses or/and necrosis – as above	≥5	≥10	absent	
		1.5–4.5	3–9	present	

ANNUBP – atypical neurofibromatous neoplasm of uncertain biological potential; MPNST – malignant peripheral nerve sheath tumour; HPF – high power field; IHC – immunohistochemistry; 1 mm^2 = about 5 HPF, in a field of 0.51 mm; # – staining used additionally in diagnosis, the morphological characteristics (mitoses, necrosis) are of primary importance

nosing MPNST formed in neurofibromas. Total immunohistochemical loss of the expression of p16, frequent in MPNST, with a low degree of histological malignancy can also be seen in atypical, and even in conventional neurofibromas, indicating that this is an early change in malignant progression, but it is not sufficient by itself to confirm malignancy. The p53 protein (product of the *TP53* gene) often accumulates in the nuclei of neoplastic cells because of its deregulation or mutation. There is no convincing data indicating that early malignant neurofibroma transformation can be detected on the basis of a slightly increased pattern of p53 expression. Moreover, in the case of cellular neurofibromas the staining for p53 is often positive, which constitutes another diagnostic trap [40–43].

Malignant peripheral nerve sheath tumor

MPNST in patients with NF1 in general fulfill the criteria of a high grade sarcoma with clear nuclear atypia with a mitotic index showing at least 10 mitoses per 10 large visual fields and frequently tumor necrosis. However, the rare cases without necrosis, with lower mitotic activity (3–9 mitoses per 10 large visual fields) should be classified as low grade MPNST (fig. 4) [40].

MPNST often show a sarcoma-like character of growth, with enlarged nuclei and a variable degree of nuclear pleomorphism. In MPNST a common phenomenon is the pattern of perivascular tumor growth, geographic necrosis with proliferation of glomerulous vessels, which resemble the appearance of a glioma (fig. 5). Heterologous differentiation similar to a rhabdomyosarcoma or osteo-chondrocytic occur in few cases and a phenotype similar angiosarcoma is rare [40].

Immunohistochemically most MPNST are negative or show focal expression for all staining of nerve sheaths with the exception of an epidermal MPNST subtype (strongly positive expression of S100 and/or SOX10). Other markers

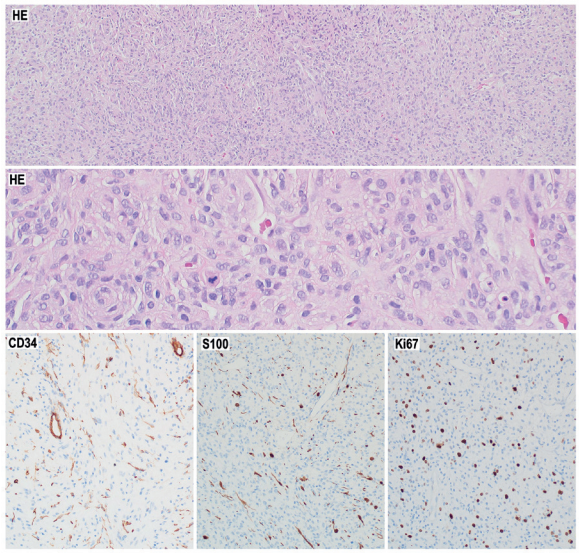

Figure 4. Low grade MPNST

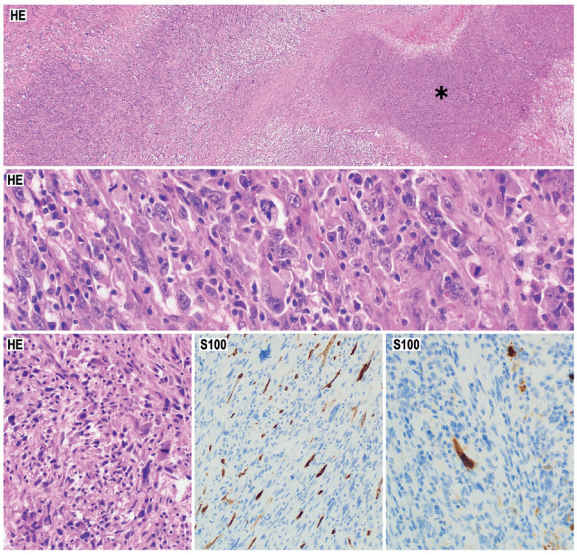

Figure 5. High grade MPNST (* – necrosis)

of Schwann cells, such as GFAP, CD57 (Leu7) and collagen IV, are characterized by a low sensitivity and/or specificity. The loss of p16 and of the CD34-positive fibroblast network are common [41]. The loss of H3K27me3 expression, due to loss of function mutations in the *EED* and *SUZ12* genes, appears to be a promising marker in MPNST diagnosis. The frequency of H3K27me3 loss varies from 30% to 90% and according to some studies is more frequent in the case of sporadic and radiotherapy associated MPNST than in MPNST developing in the course of NF1. Similarly to the evaluation of other "expression loss markers", staining of a positive internal control (mesenchymal, lymphoid or other normal cells) is necessary for a proper interpretation of the stainings. It should be kept in mind that H3K27me3 loss is not specific for MPNST and is frequently observed in in synovial sarcomas. A mosaic or heterogeneous pattern of expression (loss in some neoplastic cells) is considerably less specific and is not recommended as evidence for an MPNST diagnosis outside the typical histological and clinical context [42, 43].

In spite of considerable progress in understanding the molecular genetics of MPNST, as well as the better familiarity with the microscopic traits linked to the clinical presentation of the neoplasm, early detection of neoplastic transformation in neurofibromas associated with NF1 is still difficult, and the diagnosis of transitional lesions is still the main challenge. The introduction of the category "atypical neurofibromatous neoplasm of uncertain biological potential" is to be an introduction to the description of changes showing some microscopically troubling properties of malignant transformation, but which still do not fulfill the morphological criteria of MPNST (tab. V) [40, 41]. The introduction of more precise and objective diagnostic criteria requires the correlation of clinical, radiological, histopathological and genetic data [40, 41].

NF1 associated perturbations of various systems

The life span of persons with NF1 is on the average shorter by 10–15 years than that of the healthy population and theyhave a higher incidence of malignant neoplasms [6]. Other important clinical problems to which particular attention should be paid in caring for a patient with NF1 are:

- increased risk of vision perturbations and loss of sight (up to total blindness),
- increased probability of the occurrence of endocrinological perturbations (short stature, hypothyroidism, delayed puberty),
- increased probability of the occurrence of bone-joint, cardiovascular, neurological perturbations,
- increased probability of the occurrence of intellectual development perturbations affecting schooling readiness, limiting the choice of profession and the possibility of living independently,
- increased occurrence of perturbations of the autism spectrum and depression disorders [44, 45].

Malignant and locally aggressive neoplasms

Malignant neoplasms are the most common cause of deaths in NF1 patients, their risk of occurrence is from 2.5 to 4 times higher than the average. Malignant neoplasms which may be associated with NF1 are:

- rhabdomyosarcoma (RMS),
- neuroblastoma (NBL),
- pheochromocytoma,
- malignant peripheral nerve sheath tumor (MPNST),
- gastrointestinal stromal tumor (GIST) – in general in the form of multiple lesions located in the duodenum and the initial part of the jejunum,
- juvenile myelomonocytic leukemia (especially in patients with additional JXG type lesions),
- central nervous system tumors,
- breast cancer – women with NF1 are at an increased risk of breast cancer at a younger age and the results of treatment are much poorer than in the general population (tab. VI) [46, 47]

In persons with NF1 low grade gliomas may occur (of particular importance within the optic nerve). Because of the lack of unequivocal standards of procedure, treatment of patients in reference centers is recommended. Therapy depends on the clinical status of the patient and the maintenance of the function – e.g. of sight – strict observation is possible and if troubling symptoms occur treatment by chemotherapy with carboplatin and vincristine or monotherapy with vinblastine is initiated [48]. In patients with high grade gliomas localized treatment supplemented with temozolomide must be initiated. The average age for patients with NF1 associated gliomas is 38 years and it is lower than in the population without NF1 [49]. Another relatively common neoplasm in persons with

Table VI. Risk of occurrence of various neoplasms in children and adults with NF1

Malignant neoplasm	Risk of incidence
optic nerve glioma	15–20%
other brain tumors	>5 x increased risk
MPNST	8–13%
GIST	4–25%
breast cancer	appr. 5 × increased risk
leukemia	appr. 7 × increased risk
pheochromocytoma	0.1–5.7%
neurendocrine biliary tract neoplasms	1%
rhabdomyosarcoma	1.4–6%

MPNST – malignant peripheral nerve sheath tumor; GIST – gastrointestinal stromal tumors. Table after [46], modified

NF1 is pheochromocytoma. The frequency of occurrence is estimated as 0.1–5.7%; the median patient age is 43 years (range 14–61 years). It is multifocal in 20% of the patients and asymptomatic in 22% [50]. In care of NF1 patients attention should also be paid to symptoms associated with growing neurofibromas, which can attain considerable sizes, causing strong pain and neurological perturbations which often require a surgical intervention [51]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. Plexiform neurofibromas (PN), which may be multiple, encompass many nerve plexuses and be locally aggressive and invade surrounding soft tissues are a particular problem. Their development is unpredictable, they can have periods of rapid growth, resection is in general complicated because of the occupation of surrounding structures and rich vascularity [52, 53]. They carry an increased risk of transformation into MPNST. In 2020 in the United States a MEK inhibitor – selumetinib was registered for treating pediatric patients with symptomatic and/or progressing nonresectable PN associated with NF1. In clinical trial NCT01362803, which analyzed the effect of selumetinib on noresectable plexiform neurofibromas in the course of type 1 neurofibromatosis, children aged from 3 to 18 years took part [54–56]. Registration was performed on the basis of the above one-armed trial in 50 patients with NF1 with symptomatic, nonresectable PN. The percentage of responses to selumetinib treatment was 68% with a median time of observation of a minimum of 12 months, the median of the time of response duration was not attained. In 74% patients a decrease in tumor size by at least 20% was observed. Progression-free time was on the average 3 years [57].

This treatment is not refunded in Poland but in the case of registration of the drug should be recommended for this rare pediatric patient group (III, 2A). In a phase II trial the potential of

other systemic therapies in treating advanced PN associated with NF1 has been observed: cabozantinib or mirdametinib [58, 59].

Bone-joint perturbations

A number of perturbations can develop in the bone system in patients diagnosed with NF1, such as:

- osteopenia and the associated even five-fold increased risk of bone fractures in comparison to the healthy population. This may among others be associated with the low vitamin D levels in NF1 patients [60],
- short stature, which is a consequence of endocrinological perturbations,
- scoliosis, which affects 10–26% of the patients and often requires orthopedic procedures correcting the spinal curvature already in children,
- inborn dysplasia of the tibial bone resulting in an increased risk of fractures and the formation of pseudoarthrosis,
- dysplasia of the larger wings of the sphenoid bone,
- perturbations of muscle tone [61].

Cardiovascular perturbations

Among patients with an NF1 diagnosis cardiovascular perturbations are more common than in the general population [62]. Myocardial infarction and cerebrovascular incidents occur at a younger age in NF1 patients than in the general population. This is also a common cause of death in this group. Echocardiographic data suggest that as many as 27% patients with NF1 have a cardiovascular anomaly and a constriction of the lung artery is responsible for 50% of these anomalies. Because of this, all children born with NF1 should undergo a detailed cardiological examination, and if any irregularities are observed should be under the supervision of cardiological clinics [63].

Vascular diseases associated with NF1 include among others a constriction of renal and cerebral arteries, aorta coarctation and arterial and venous malformations. Vasculopathies in general concern the arterial system and lead to a disease of cerebral vessels (e.g. constriction or dilation of vessels, aneurysms) or a constriction of the renal artery. The frequency of vasculopathy occurrence in NF1 is 0.4–6.4%. Changes in cerebral vessels occur in 2–5% and are associated with an increased risk of hemorrhagic strokes occurring both in children and in adults [64]. Renal artery stenosis often manifests as arterial hypertension, which should be regularly monitored in persons with NF1. Early detection of arterial hypertension is important because of the possibility of preventing complications, moreover, each patient with unexplained arterial hypertension should be examined for renal stenosis and pheochromocytoma [63, 65].

Dermatological lesions

In care for NF1 patients attention should also be paid to symptoms associated with growing neurofibromas, which can attain large sizes and cause very strong pain, bleeding, perturbation of functions, prurits, deformations and neurological perturbations. In such cases a surgical intervention is necessary [66]. The numer of neurofibromas was found to increase with age and in pregnancy (in 33–60% of pregnant women the numer of lesions increases) [67, 68].

In about 70% patients pruritus (mainly in the evenings) may occur which does not react to antihistamine treatment. Pruritus is generally localized in the affected areas. In such a situation treatment similar to that used in neuropathic pain (e.g. gabapentin) can be considered. *Café au lait* spots and freckles do not require treatment [69].

Neurological perturbations

Patients with NF1, in whom a new cognitive deficit occurs should be evaluated both for cerebral vascular disease and the occurrence of primary brain tumors. Patients with epileptic fits or progressive macrocephaly should be diagnosed as rapidly as possible for brain tumor development or hydrocephalus. In particular, children in whom an increase in head circumference is observed should be evaluated for hydrocephalus or CNS neoplasms. An analysis has shown that in children and adults with NF1 (n = 8579) – in comparison to a control group (n = 85 790) – headaches, Parkinson disease and sleep perturbations are more common [70].

Cognitive function perturbations

Cognitive function perturbations are typical in children with NF1 and are maintained in adults, causing poorer results in school and a lesser chance for employment. Research has shown that in comparison to the general population the IQ in adults with NF1 can be lower to a similar extent as in children with this disease. In 20 adults with NF1, who were compared to a control group, deficits in spatio-visual abilities, memory, attention and executive functions were observed [71]. A microdeletion of the NF1 gene is believed to be associated with a stronger intellectual disability [72]. Moreover, research has shown that 30–55% of adults with NF1 have depression or have other psychological problems [73]. Attention deficit hyperactive disorder (ADHD) is found relatively frequently already in the pediatric population with NF1 [74]. These persons were also found to have a significantly lower quality of life and emotional control than persons with ADHD alone or NF1 alone [75].

Proposed scheme of control examinations of children and adults

The details of control examinations depending on age are presented in table VII [76]. Imaging studies are performed with various frequencies depending on the clinical symptoms – more often in younger patients, less often in older ones – in general one a year [76]. A patient with an NF1 diagnosis should be under the care of a multi-specialist team until the end of their life [47]. Care for adult patients from a given region should be provided in coordinating centers created in particular voivodeships in the scope of the National Oncological Network.

Table VII. Details of control examinations depending on the patient's age after [76]

Age	Examination during medical visit
first month of life	• evaluation of skin lesions, of the muscle and skeletal systems, opthalmological and neurological examination • examination of parents for NF1 symptoms (if not done previously) • some specialists recommend a preliminary imaging study to detect optic nerve glioma
first years	• body weight, height and head circumference measurements • evaluation of skin lesions, of the muscle and skeletal systems, opthalmological, neurological, cardiological or other examinations (if indicated) • psychological counselling for the parents
2–5 years	• body weight, height measurement • evaluation of skin lesions • opthalmological, neurological, cardiological or other examinations (if indicated) • evaluation of hearing, psychomotor development (speech, concentration, memory, psychological problems)
5–13 years	• body weight, height measurement • evaluation of skin lesions • opthalmological, neurological, cardiological or other examinations (if indicated) • evaluation of sexual maturity • collecting information concerning school performance (difficulties with learning, hyperactivity, behavioral problems, perturbations of concentration and memory) • analysis of social adjustment • discussing the effect of puberty on the development of the disease
from 13 years	• opthalmological, neurological, orthopedic examination once a year and other examinations (if indicated) • control of arterial blood pressure • evaluation of sexual maturity • genetic and, psychological counselling, if required pain management clinic • control in objective and subjective examination and if required imaging studies to look for secondary MPNST and other neoplasms • from 30 years of age control in women for breast cancer • consider supplementation with vitamin D

It should be kept in mind that if type 1 NF is found in a child, both parents should undergo examination. If a parent is affected, all children in the family should be examined for NF1. Affected parents should be informed that for each pregnancy the risk that the child will be affected is 50%.

Control examinations in adults

In adults particular attention should be paid to selecting patients with NF1 with a "high risk" phenotype. This is the group of patients in whom there is a high probability MPNST development [79]. Risk factors are the presence of numerous lesions of the neurofibroma type associated with peripheral neuropathy and the presence of at least one internal neurofibroma. The NF1 scale allows the selection of patients who have a higher probability of developing internal changes of the NF1 type (tab. VIII) [78].

In patients with a high point count imaging studies (preferably MRI) should be performed to search for suspicious lesions. They should be monitored at least once a year. The remaining patients should be monitored by a qualified specialist group once every 2–3 years, and by basic care physicians, internists and dermatologists once a year [45]. Women with NF1 require earlier screening (from 40 years) for breast cancer [7, 9].

Genetic counseling

As NF1 is inherited in an autosomal dominant manner, genetic counseling should be provided for the patients and their families. The risk of the disease is 50% for each child of an affected parent. The couple should also be informed that the risk of having an affected child can be decreased by the use of reproductive technologies, including oocyte or sperm donation, depending on the affected parent [61].

Treatment of MPNST associated with NF1

Radiological diagnosis

Type 1 neurofibromatosis (NF1) is a syndrome which is characterized by a very broad spectrum of clinical symptoms and an increased incidence of neoplasms. The course of the disease can be different in individual patients, which is associated with the need to use diverse imaging methods depending on the region of the body affected by the disease as well as the relevant clinical symptoms [77, 78]. Imaging studies play an important auxiliary role in diagnosis and monitoring the course of the disease (e.g. evaluating the extent of the lesion before beginning treatment or observing progression after completing the treatment), however, the basic diagnostic method is still clinical evaluation, which is the basis for further procedures. Routine imaging studies in patients with NF1 are not recommended [22, 79]. Magnetic resonance should be used mainly for clinical suspicion of the presence of a tumor [80].

Neurofibromas are benign neoplasms derived from Schwann cells – in imaging studies they are visible as well delimited oval tumors. In MR analysis in T_2-dependent sequences they often present a so-called "shooting target symptom"

Table VIII. NF1 scale

NF1 scale	
independent factors associated with the occurrence of internal NF	**points**
age ≤30 years	10
presence of skin NFs	10
≥2 subcutaneous NFs	15
<6 *café au lait* spots	5
Probability of occurrence of internal neurofibromas	
NF1 points	**probability (%)**
0	5.1
5	8.3
10	13.3
15	20.7
20	30.8
25	43
30	56.1
35	68.4
40	78.7

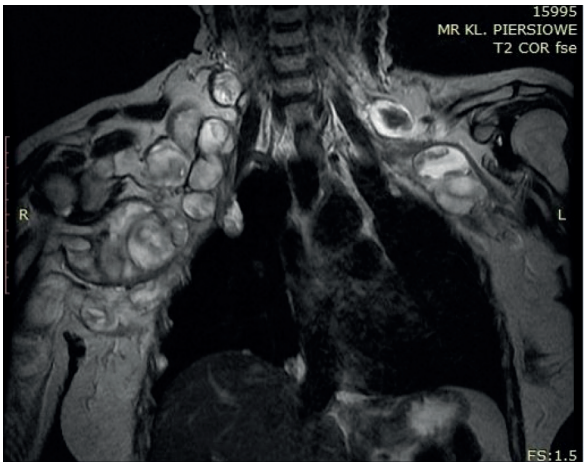

Figure 6. Type 1 neurofibromatosis. MR in a T_2W sequence showing the occurrence of multiple neurofibromas. Typical appearance of neurofibromas with visible symptom of a "shooting target"

(the center of the tumor with a low signal surrounded by a high signal border), after administration of a contrast agent they undergo non-homogeneous amplification (fig. 6). It should, however, be kept in mind that MR diagnosis is mainly indicated in the case of a clinical suspicion of a malignant neurofibroma transformation to MPNST (fig. 7). The risk of formation of MPNST in patients with NF1 (most commonly adults) is about 8–13% [81]. Among symptoms suggesting a malignant neurofibroma transformation are persistent pain, rapid growth and change of consistency of the tumor (from elastic to hard). MPNST is most commonly localized deep in soft tissues, near the nerve trunk – in T_1- and T_2-dependent sequences, with the presence of high-signaling areas in T1W images, which is helpful in differentiation from benign neurofibromas (fig. 6) [82]. MPNST show irregular, most commonly marginal contrast intensification with the possible coexistence of cystic lesions within the tumor and edema in the surrounding soft tissues. It should, however, be kept in mind that the value of imaging studies in the evaluation of the extent of plexiform neurofibroma in the absence of evidence for tumor progression is still debatable and treatment is generally based on an unequivocal determination of clinical progression. For this reason decisions about whether

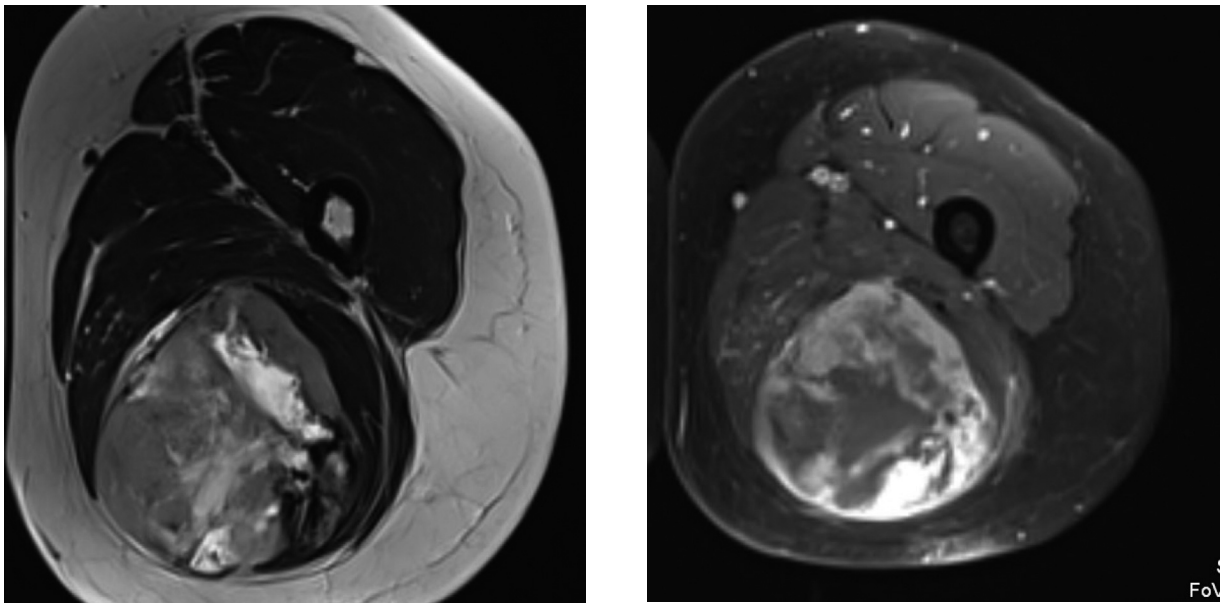

Figure 7. Malignant peripheral nerve sheath tumor (MPNST). Malignant transformation of neurofibroma in a patient with diagnosed NF1. MR in a T_2W sequence and T_1W *fatsat* with intravenous contrast agent showing a non-homogeneous tumor undergoing a pathological contrast intensification with visible areas of necrosis

and when imaging studies should be performed should best be left to physicians experienced in care for NF1 patients [22].

In patients with NF1 it is noteworthy that other soft tissue sarcomas such as rhabdomyosarcoma or other malignant neoplastic processes (e.g. acute myelocytic leukemia, phaeochromocytoma or breast cancer) are more common [83]. Renal phaeochromocytomas are rare in children with NF1. Most experts recommend screening for phaeochromocytoma if a clear increase occurs in the frequency of heart action and/or blood pressure, but do not recommend them for asymptomatic patients. In patients with NF1, phaeochromocytomas are often detected by chance in examinations performed during evaluation or monitoring of another neoplasm [84]. They appear most commonly as large, heterogeneous tumors showing areas of disintegration and cystic lesions. Typically they show a very strong contrast intensification. MR is the most sensitive imaging method in phaeochromocytoma diagnosis (sensitivity 93–98%, specificity 93%). A characteristic property is the appearance of a clearly high signal in T_2-dependent images – the so-called lightbulb sign [85].

MRI is the most popular method of visualizing the lesions within the brain. Among the most common pathologies occurring in the central nervous system is the presence of foci characteristic for NF1 with a high signal in T_2W and flair images, so-called UNO (unidentified neurofibromatosis objects) or FASI (focal abnormal signal intensity), occurring most commonly within basal ganglia, the midbrain and the cerebellum in children and teenagers (fig. 8) [86–88]. Lesions should not show an additional effect of mass nor pathological signal intensification. If this occurs transition to a glioma should be suspected [89]. UNOs most commonly undergo spontaneous regression in the second decade of life, however, some of the lesions occurring mainly the middle parts of the frontal lobes and in the thalamus, may be maintained in adults, which is probably due to a different basis for their presence a [87]. Low grade gliomas can occur in any brain localization but are often observed in the brain stem.

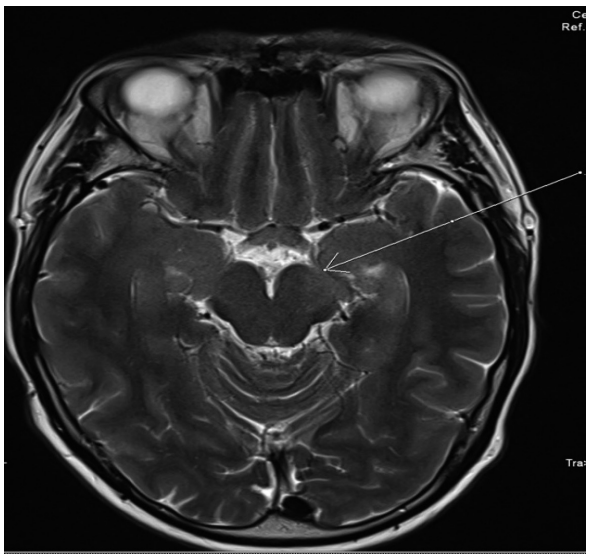

Figure 8. MR of the brain. Areas typical for NF1 with a high signal in T_2W and Flair images most commonly occurring within basal ganglia, the midbrain and the cerebellum, the so-called UNO (unidentified neurofibromatosis objects) or FASI (focal abnormal signal intensity)

The most common neoplasm of the CNS associated with NF1 is optic pathway glioma (OPG) (fig. 9) [80]. This is a low grade neoplasm (pilocytic astrocytoma WHO 1), often asymptomatic and growing slowly. However, in some cases perturbations of vision may occur and in advanced stages exophthalmos and perturbations of eyeball mobility and occupation of the hypothalamus, which may manifest as premature puberty. The risk of occurrence of an asymptomatic form of OPG is the highest in children up to the age of 7, however, routine MR examinations are not encouraged in asymptomatic children [81]. In imaging studies these tumors are characterized by an enlargement and thickening of optic nerves and the visual pathway, with possible occupation of optic nerve chiasm show an elevated signal in T_2W images, may also cause an increase in contrast (especially during treatment). Regular imaging studies of the brain are not recommended in asymptomatic children. A single initial MR of the brain remains optional [80]. During the transition into adulthood a single whole-body MR Is recommended [81].

Indications for imaging studies in patients with NF1:

- focal sensory or motor symptoms,
- epileptic episode,
- headaches (with increasing frequency and intensity),
- symptoms of increased intracranial pressure,
- TIA, stroke-like symptoms,
- visual perturbations (worsening of vision acuity or of the visual field),
- premature puberty, accelerated growth,
- growth of neurofibroma and/or appearance of pain,
- encephalopathy symptoms or worsening of cognitive functions,
- limb asymmetry,
- increase of arterial tension and/or pulse.

Musculo-skeletal perturbations associated with NF1 encompass among others macrocephaly, short stature and osteopenia, scoliosis, and also bone dysplasia. Dysplasia of long bones, dysplasia of sphenoid bone wings or scoliosis are another manifestation of NF1, though they are relatively rare (in about 10% of patients with NF1), may cause an increased incidence and complications [90, 91]. Most commonly in the diagnosis of these lesions normal X-ray images are sufficient, whereas computed tomography or magnetic resonance are used in particular cases. More frequent occurrence of a broad range of inborn cardiac problems is associated with NF1 , a higher risk of the occurrence of vascular pathologies such as stenoses and aneurysms in younger patients and atherosclerosis in older ones. The lesions most commonly concern the aorta, carotid arteries, mesenteric arteries. Stenosis of the renal artery occurring in patients with NF1 is a well-known cause of arterial hypertension. In order

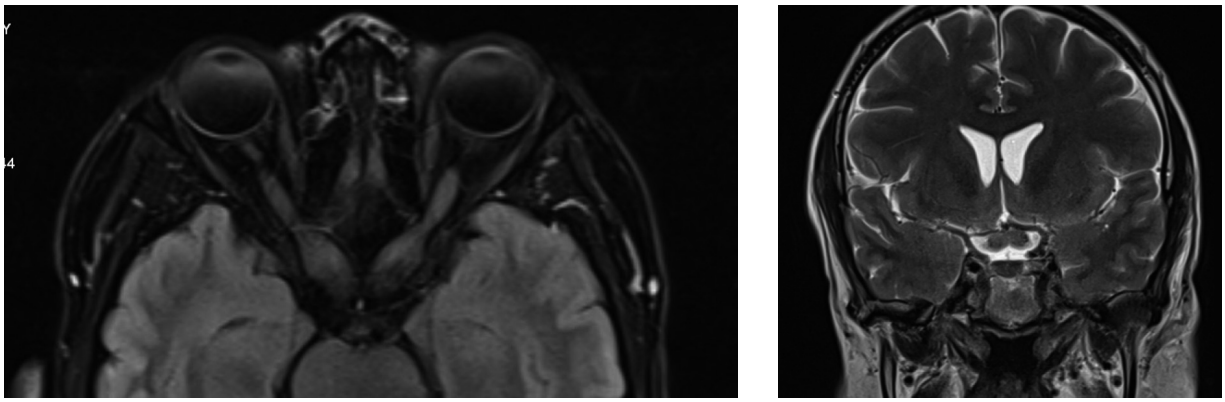

Figure 9. Glioma of optic nerve chiasm in a 27-year-old patient with NF1. MR, flair sequence in transverse section w and T_2W sequence in frontal section show clear, symmetric thickening of the optic nerves

to diagnose these lesions ultrasonographic and angiographic analyses are performed (TK, MRI or DSA) [63].

[^{18}F]-FDG PET with the use of CT or MR is being used with increasing frequency in patients with NF1 in the case of a suspicion of malignant tumor transformation, in order to determine the degree of progression and to monitor the response to treatment. This is usually [^{18}F]-FDG PET/CT. [^{18}F]-FDG PET analysis with the use of the CT or MR modality is increasingly being used in diagnosis, biopsy, determination of degree of progression and monitoring the response to treatment of patients with NF1. The use of the modality of magnetic resonance [^{18}F]-FDG PET/MR may increase the value of the imaging and decreases the exposure of the patient to ionizing radiation. Because of the rare occurrence of the disease, so far there are no prospective studies on a larger group evaluating the value of [^{18}F]-FDG PET in patients z NF1. For this differentiation of malignant from benign lesions the most commonly used is the SUV index (standard uptake value). Most studies indicate that SUV ≥ 3.5 indicates the diagnosis of a malignant lesion. The determination of the optimal SUV cutoff value is made difficult because of the differences between scanners. Using the quotient of the SUV index tissue/liver (T/L) may eliminate the difference between scanners, but the optimal value of the T/L index has not been defined. The use of repeated PET-CT with a delay increases the diagnostic value but also in parallel the costs and exposes the patient to ionizing radiation [92, 93].

Indications for a biopsy

A clinical suspicion of MPNST (rapid growth of a soft tissue tumor in a patient with NF1, especially with a subfascial localization) and in imaging studies requires determining a histopathological diagnosis before definitive treatment. For this purpose a thick needle – or in exceptional cases – an open biopsy is indicated [94, 95].

Treatment

About 30–50% of MPNST cases are associated with NF1. The risk of MPNST occurrence in patients with NF1 is 8–13% compared to 0.001% in the general population. In this group of patients MPNST is generally diagnosed at the age of 20–40 years, compared to 30–60 years in the general population. Some MPNST, in particular of the head and neck region, may be secondarily induced by prior radiotherapy because of other neoplasms, for instance optic pathway gliomas [96–98]. The risk of MPNST development increases by as much as 20-fold within plexiform neurofibromas [99].

The results of treatment and prognoses for patients with MPNST associated with NF1 are similar as for the general population. Some retrospective analyses have shown shorter survival for patients with MPNST associated with NF1 [100–102]. However, other studies did not confirm significant differences [103–105]. Because of the lack of unequivocal data concerning differences in prognosis, the procedure recommended for treating MPNST associated with NF1 is in agreement with general guidelines for MPNST treatment. Qualification of patients for treatment should be done by a multispecialist panel [106, 107].

Surgery in MPNST

In the case of an MPNST in a patient with NF1 the therapeutic procedure should not differ from the general principles of treating soft tissue sarcomas. The main aim in treatment is to provide local control of the disease. A definite cure can only be obtained by total macro- and microscopic surgical treatment (II, 1) [94, 95]. The extent of the surgery is determined by such factors as tumor localization and size, infiltration of surrounding structures (blood vessels, nerves) or the need to apply reconstructive techniques. In the case of MPNST, the nerve trunk from which it is derived must be removed, and in patients with NF1 this may be considerably overgrown [108, 109].

Perioperative treatment

The standard perioperative treatment in patients with MPNST conventionally fractionated pre- or postoperative radiotherapy (II, 2A). Its aim is to improve the local control or enabling the surgery in the case of locally advanced tumors. During qualification of patients and planning radiotherapy, current national

and international recommendations for treatment of soft tissue sarcomas should be taken into consideration. The guidelines of the American Society for Radiation Oncology (ASTRO) for the first time recommended preoperative over postoperative radiotherapy in patients without significant factors for impaired wound healing after resection [110–114]. Locally advanced MPNST, including radiation-induced MPNST should be treated, if possible, within prospective clinical trials based on combined conventionally fractionated or hypofractionated radiotherapy with systemic treatment or other methods increasing local effectiveness such as hyperthermia [115–117]. It is important to consider the higher risk of inducing secondary neoplasms after radiotherapy in the course of NF1, which is particularly important in the case of the group of young patients treated with a radical intention [118].

In selected cases of MPNST, perioperative treatment in agreement with general guidelines for treating soft tissue sarcomas should be applied [119]. Preoperative chemotherapy should be considered if there is a risk of tumor non-resectability ascertained on the basis of radiological analysis or in patients in whom rapid decrease of the tumor mass is important e.g. one pressing on surrounding nerves and causing strong pain (II, 2A). Single analyses indicate an improvement of resectability after applying preoperative chemotherapy in particular in children [120]. In agreement with the results of trial ISG-STS 1001, which indicated that chemotherapy adapted to the histological type of the sarcoma (in the case of patients with MPNST this was a combination of ifosfamide and etoposide) increases the recurrence or death risk, the use of 3 cycles based on a combination of anthracyclines and ifosfamide is preferred (II, 2A) [106, 121, 122].

Monitoring after MPNST treatment

The possibility of MPNST occurrence should in particular be kept in mind when constant pain develops in an NF1 patient, rapid increase in neurofibroma size, change from soft to hard consistency or a neurological deficit appears [123].

After MPNST treatment in a patient with NF1 the observation procedure should not differ from general principles of observation of patients after treatment of high grade soft tissue sarcomas and encompasses:

- regular physical examination,
- observation of the scar after resection of the primary focus using USG or magnetic resonance,
- observation using X-rays or/and computed tomography to look for distant metastases, in particular to the lungs [113].

Treatment of metastatic disease

Chemotherapy is the basis for treating metastatic disease. It should, however, be kept in mind that MPNST is considered to have a low sensitivity to chemotherapy and the results of treatment with cytostatics are unsatisfactory. If such a possibility exists, the participation of the patients in prospective clinical trials should be suggested. In the case of disease with a limited number of metastases, local treatment should be considered, that is surgery and/or radiotherapy (IV, 2A).

As MPNST diagnoses are rare, data concerning the effectiveness of particular chemotherapy regimens are based on metaanalyses of patients treated in clinical trials concerning various soft tissue sarcomas and also on retrospective analyses of patients treated in reference centers [106].

Analysis of 12 clinical trials run by the European Organisation for the Research and Treatment of Cancer (EORTC) indicated that using the AI combination (doxorubicin with ifosfamide) was associated with a longer, but statistically insignificant, progression-free survival (PFS) in comparison with patients treated by anthracycline as monotherapy (26.9 *vs.* 17 weeks) and the highest percentage of objective responses [124]. Monotherapy with anthracycline has PFS similar to regimens together with ifosfamide, which justifies using this treatment procedure, particularly in patients in whom the main aim of the therapy is control of metastatic disease (III, 2A). Numerous retrospective analyses also confirm the highest efficacy of regimens based on anthracyclines [102, 125–127]. If the aim of the treatment is alleviating pronounced symptoms, associated for instance with infiltration and pressure on the nerves or obtaining potential resectability of the tumor and/or the metastases, adding ifosfamide to doxorubicin seems justified. In choosing the chemotherapy regimen in clinical practice its toxicity should also be taken into consideration. The combination of doxorubicin and ifosfamide is more myelotoxic in comparison with doxorubicin in monotherapy. It should be kept in mind that during treatment with regimens based on anthracyclines, radiotherapy should be used with great care due to the risk of increased toxicity, in particular during irradiation of the chest [128].

Another regimen showing some effectiveness in patients with MPNST, which can be considered in successive lines of treatment is etoposide combined with ifosfamide (IV, 2B) [125, 129]. Besides classical chemotherapy, among targeted drugs pazopanib has shown some effectiveness in advanced MPNST (IV, 2B) [125, 130]. Clinical trials using targeted therapies and/or immunotherapy are ongoing.

Conclusions

Type 1 neurofibromatosis (NF1) is one of the most common genetic perturbations inherited in an autosomal dominant manner. Persons with NF1 generally come to a physician with characteristic pigment perturbations (*café au lait* type spots, skinfold freckles, Lisch nodules) but they are also prone to the development of many other clinical problems, including bone defects (deformation of the tibia and pseudoarthrosis, dysplasia of sphenoid bone wings), cognitive impairment, behavioral perturbations and specific difficulties in learning and benign and malignant nervous system neoplasms (neurofibromas, malignant neoplasms of peripheral nerve sheaths, optic nerve gliomas). Since the identification of the *NF1* gene

and its protein product, neurofibromin, numerous data from laboratory and clinical studies have led to a better insight into the mechanisms underlying the bases of pathogenesis and disease progression and have indicated new therapeutic targets. While the basis of care for patients with *NF1* mutations is surveillance according to guidelines appropriate for their age, recent trials encompass the identification of prognostic factors for the development of particular clinical characteristics of NF1 and the severity of the course of the disease which in the future may lead to a more personalized care for the patients.

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