Malignant Peripheral Nerve Sheath Tumors (MPNST) in Neurofibromatosis Type 1 (NF1): Diagnostic Findings on Magnetic Resonance Images and Mutation Analysis of the NF1 Gene

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Abstract. Plexiform neurofibroma (PNF) is a typical feature of neurofibromatosis 1 (NF1). About 10% of patients with NF1 develop malignant peripheral nerve sheath tumors (MPNST), usually arising from PNF, and this is the major cause of poor prognosis. A better prognosis can be achieved if the tumors are diagnosed at an early stage. Our objective was to establish magnetic resonance imaging (MRI) criteria for MPNST, and to test their usefulness in detecting early malignant changes in PNF and to correlate the findings with the mutations of the NF1 gene. Patients and Methods: NF1 outpatients were diagnosed according to the NIH criteria. All patients underwent a complete dermatological, ophthalmological and neurological examination and ultrasound of the abdomen between 1997 and 2002. The study was approved by the Institutional Review Board and all patients gave informed consent to analyze clinical records and tumor material for scientific purposes. MRI was performed with devices at 1.5 Tesla field strength (Siemens Magnetom Symphony) or in some patients at 1.0 Tesla field strength (Siemens Impact Expert). T1- and T2-weighted sequences including STIR-sequences were acquired. Ultra-rapid image sequences with HASTE technique were performed for trunk imaging. In patients with no contraindication for the application of contrast media, Gadolinium-DTPA Magnevist was administered intravenously. Results: MRI was performed on 50 patients with NF1 and nerve sheath tumors, of whom 7 had atypical pain, tumor growth or neurological deficits indicative of malignancy; the other 43 were asymptomatic. On MRI, all 7 symptomatic patients had inhomogeneous lesions, due to necrosis and hemorrhage and patchy contrast enhancement. In one patient, the multiplicity of confluent tumors with inhomogeneous areas in addition to central lesions did not allow the exclusion of malignancy. Only 3 of the 43 asymptomatic patients had comparable changes; the other 40 patients had tumors of relatively homogeneous structure on T1- and T2-weighted images before and after contrast enhancement. All 3 asymptomatic patients with inhomogeneous lesions were shown to have MPNST. Analysis of mutations of the NF1 gene of the 10 MPNST patients revealed a variety of mutations. Concerning the correlation of genetic findings and MPNST in NF1, the sample size of this study group was too small to define genotype-phenotype relations. In this cohort, all types of mutations were found. Conclusion: This study provides evidence for certain radiographic findings on MRI in PNF of NF1 patients that have to be considered as signs of malignancy, in particular indicating an MPNST. These findings are especially valuable in the long term follow-up control of patients with large tumors (plexiform neurofibromas).

Neurofibromatosis 1 (NF1) is an autosomal dominant disease with an incidence of about 1 in 3,500 humans. NF1 is caused by mutations of the NF1 tumor suppressor gene (OMIM 162200) located on chromosome 17q11.2 (2, 20). NF1 patients can develop a plethora of signs and symptoms. Benign and malignant lesions like neurofibromas, pilocytic astrocytomas and malignant peripheral nerve sheath tumors (MPNST) characterize NF1 as a disease with increased risk of tumor development. Indeed, the development of tumors in NF1 follows the two-hit model for a tumor suppressor
gene (13). Somatic loss or mutation of the normal \( \text{NF1} \) allele has been found in different tumor entities of NF1 patients, e.g. cutaneous or plexiform neurofibromas (PNF), pilocytic astrocytomas and MPNST (3, 17-19, 14, 8-12). MPNST are highly aggressive neoplasms of Schwann cell origin. It is assumed that about 50% of all MPNST develop in NF1 patients. The lifetime risk of developing a MPNST is 8 – 13% among NF1 patients, with a 5-year survival rate of only 21% (5). MPNST are a leading cause of death in NF1 patients (16). This entity responds poorly to chemo- or radiotherapy, with surgical ablation with wide resection margins being the only effective therapeutic option (21).

A recently published study on NF1 patients suggested that those patients with a megabase deletion of the entire \( \text{NF1} \) locus develop a MPNST more frequently than NF1 patients with other kinds of constitutional mutations (4). Wu et al. (22) presented 7 NF1 patients with MPNST, of whom 3 patients had constitutional mutations and 3 had deletion of the whole \( \text{NF1} \) gene. In this study, we compared the constitutional \( \text{NF1} \) gene mutation with MRI findings. The aim of this study was to compare the mutation type of MPNST and the appearance of these tumors on magnetic resonance imaging (MRI) scans in order to find out whether the types of mutation correlate with the image of the tumors.

**Patients and Methods**

MRI. MRI was at 1.5 or 1.0 Tesla, with T1- and T2-weighted sequences including a short-\( T \) inversion recovery (STIR)
The updated version by the Fédération National des Centres de tumor differentiation was scored according to histological type in accordance with the National Cancer Institute (USA) system and presence of rhabdomyoblasts. Histological grading was determined by the mitotic rate, size of necrotic areas, nuclear pleomorphism and the diagnosis was based on the light microscopic features of cellularity, mitotic rate, size of necrotic areas, nuclear pleomorphism and the presence of rhabdomyoblasts. Histological grading was determined according to the National Cancer Institute (USA) system and tumor differentiation was scored according to histological type in the updated version by the Fédération National des Centres dé Lutte Contre le Cancer.

**Morphology.** For patients 1 and 8, an amputated limb was available for macroscopic investigation. The correlation of MRI images and macroscopic and microscopic findings was carried out on these specimens. Immunohistochemical and light microscopic studies were performed on formalin-fixed, paraffin-embedded tissues. DNA was extracted from blood lymphocytes using a QIAamp Blood Kit from Qiagen (Hilden, Germany). Mutation analysis was performed by direct sequencing of 57 constitutive NF1 exons (6, 10, 12). Primers for exon 12b were designed in this study. Several primers were from Abernathy et al. (1) and Fahsold et al. (6). All mutations were confirmed by repeat amplification and sequencing (12).

**Results**

The diagnosis of MPNST was suggested clinically in 7 patients. This diagnosis was suggested in a further 3 patients, based on MRI findings only. All patients had inhomogeneous tumors (Figure 1). The inhomogeneity became more evident after contrast enhancement. In one patient, the multiplicity of confluent inhomogeneous tumors did not allow us to exclude malignancy.

The family history of the patients revealed 2 with a parent with NF1 who died from MPNST. Five patients had a high internal tumor burden that became visible on MRI. One patient developed an MPNST 10 years after the first diagnosis of this entity.

Genetic analysis of the blood of these patients was informative in 8. The mutation types varied considerably and showed no apparent predilection for any type associated with MPNST (Table I).

**Discussion**

Patients with NF1 who develop a MPNST have different mutations of the NF1 gene but share some characteristic findings that can be identified on MRI. In this small cohort, MPNST in NF1 patients frequently showed inhomogeneous contrast enhancement. This inhomogeneity correlated to regions of necrosis and hemorrhage alternating with areas of solid tumor. This correlation was proven macroscopically during tumor surgery and on histological sections of resection specimens, in particular on the preparations of 2 amputated limbs of 2 of our patients. Interestingly, in 3 patients the MPNST was detected in the PNF on follow-up MRI, even though the patients did not have significant clinical features. The diagnosis was made from changes on the images, in particular the new findings of inhomogeneous contrast enhancement areas inside the (large) PNF.

**Conclusion**

MPNST in NF1 share some findings that can be used for differential diagnosis in follow-up controls, in particular in those patients with large tumors. The mutations of the NF1 gene varied considerably and showed no predilection for any type. However, in larger series megabase deletions were found to be significantly associated with MPNST in NF1 (12).

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**References**


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