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Original article

# Quantitative microstructural cerebral changes in neurofibromatosis type 1

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**Abstract**

*Objectives:* To evaluate microstructural cerebral changes in children with neurofibromatosis type 1 (NF1) based on $T_2$ relaxation time measurements at 3Tesla.

*Methods:* From our dataset of pediatric MRI examinations at 3T 19 pediatric NF1 patients (1.9–14.3 years of age, 9 girls, 10 boys) were retrospectively selected and compared with the previously published group of 44 healthy children (0–16 years of age). MRI examination included a triple echo TSE sequence as basis for $T_2$ maps. $T_2$ relaxation times were measured in 37 brain regions.

*Results:* Compared with healthy controls, $T_2$ relaxation times had the tendency to be increased by 1.01% (GM) to 11.85% (dentate nucleus) for NF1 patients. Only in posterior limb of the internal capsule and parietooccipital white matter values were reduced. No differences were observed between both hemispheres. Overall, no strong evidence supporting a difference between NF1 patients with and without optic glioma or with normal and impaired neuropsychological development was observed.

*Conclusions:* Using $T_2$ relaxation times it was possible to describe measurable microstructural differences in multiple brain regions between NF1 patients and healthy children regardless of whether signal abnormalities were visible on conventional images.


*Keywords:* Neurofibromatosis type 1; Magnetic resonance imaging; Quantitative imaging; T2 relaxation time; Children; Brain

## 1. Introduction

Neurofibromatosis Type 1 (NF1) is a common neurogenetic autosomal dominant disorder with a world-wide incidence of 1 in 2500–3000 individuals [1]. In addition to typical diagnostic clinical features, MR imaging plays an important role in evaluation of NF1 patients. Around 15% develop optic pathway gliomas [1] and 40–93% show focal T2-hyperintense parenchymal lesions especially in the basal ganglia, thalamus, brainstem, cerebellum and subcortical white matter [2–11]. These lesions have been described as unidentified bright objects (UBOs) or focal areas of signal hyperintensities (FASI). Their origin is still unclear [12–14]. However, taken together with the observation that 40–60% of NF1 patients have a learning disability, they suggest that NF1 patients may suffer abnormal brain development. For example, Moore et al. [8] already published

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greater gray matter volume as well as greater gray: white matter ratio in NF1 patients in comparison to controls. Apart from optic pathway gliomas and possible signal alterations, conventional MR imaging is unremarkable in most cases, although it should be kept in mind that slight signal abnormalities can be difficult to detect especially in early cerebral development. Thus, the question arose whether further microstructural changes, even in normal appearing brain structures, are present in NF1 patients and whether quantitative MR imaging enables more sensitive detection. In contrast to previous studies describing microstructural changes between UBOs and normal appearing brain regions, we measured $T_2$ values for the first time in different defined supra- and infratentorial brain regions regardless of whether they showed signal abnormalities and compared them with normal controls.

## 2. Material and methods

This retrospective study was approved by the local institutional review board. Written informed consent was obtained from all patients in this study. From our database of pediatric MRI examinations, we retrospectively selected all pediatric NF1 patients scanned at 3 Tesla (Magnetom Verio, Siemens, Erlangen, Germany). 19 patients (9 females, 10 males, age range: 1.9–14.3 years, 9 with and 10 without optic glioma) with NF1 diagnosis based on clinical criteria were included. Six patients showed normal cognitive development, six patients showed mild learning difficulties or behavioral disturbances, and six patients had marked impairment necessitating support. In one case, examined because of suspected hearing loss, further clinical data were missing. The previously published group of 44 children [15,16] with age appropriate neurological development and normal neurological findings on clinical examination served as the control group. NF1 patients as well as the control group were examined at the same scanner using identical, routinely performed axial triple echo turbo spin echo sequences with the following parameters: slice thickness of 3 or 4 mm, TR/TE1/TE2/TE3 = 6920/8.7/70/131 or 5120/8.7/70/131 (TR = repetition time and TE = echo time in ms) and turbo factor of 6. As described earlier by Ding et al. [17], $T_2$-maps were generated. Using manually delineated ROIs with a fixed size between 20 and 40 $mm^2$, $T_2$ relaxation times were measured in the following 37 cerebral locations (Table 1).

These regions were examined no matter whether they showed signal abnormalities or normal appearance on conventional images. An experienced neuroradiologist (E.B.) carefully selected anatomically comparable ROI positions on proton or $T_2$ weighted images. Using the program imageJ (based on Java, public domain https://imagej.nih.gov/ij/) ROIs were transferred to $T_2$-maps. For each ROI mean $T_2$ value and standard deviation were calculated and expressed in milliseconds. In 5 examinations, particular ROIs had to be excluded due to motion artifacts or partial volume effects.

## 3. Statistical analysis

Initially, demographic and baseline characteristics were analyzed descriptively for each group (i.e., healthy children and NF1 patients, NF1 patients with and without optic glioma). To investigate differences in $T_2$ relaxation times during brain maturation between healthy and NF1 children in each cerebral region of interest, multivariable linear regression models for each brain region were implemented, as already published [15,16]. Regression analysis results are presented using point estimates of parameters with 95% confidence intervals. Evidence of change on $T_2$ regarding age and health status (diseased versus healthy children) was concluded at significance level 5% when 95% confidence interval did not include value zero of no difference (coinciding with p-value less than 5%). In order to compare left with right side of each brain region, a two-sided *t*-test was implemented to test the null hypothesis of no difference at significance level 5%.

Since the group of healthy children included much younger patients than the group of NF1 children, we decided to exclude children younger than 20 months from the healthy group and repeated analysis.

$T_2$ relaxation times for NF1 patients with and without optic glioma, as well as for NF1 patients showing normal versus impaired neuropsychological development were analyzed in similar fashion.

All statistical analyses were conducted using SAS 9.3.

## 4. Results

### 4.1. Demographic and baseline characteristics

Baseline and group characteristics for 44 healthy control children and 19 NF1 patients were analyzed descriptively and are presented in the Appendix (Table A1). Gender was similarly distributed in both groups. Median age was 8.9 years for NF1 patients compared to 2.9 years for the healthy group. Due to different age distribution we excluded 19 healthy children younger than 20 months. After exclusion, median age for the healthy group increased to 7.5 years. 9 NF1 patients showed an optic glioma compared to 10 patients without optic glioma.

### 4.2. Comparison of T2 relaxation times between healthy and diseased children

Overall, $T_2$ relaxation times had the tendency to be increased in all regions in NF1 patients compared to

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