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Ultrasound assessment of peripheral nerve pathology in neurofibromatosis type 1 and 2

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HIGHLIGHTS

- Ultrasound is an easy-to-apply tool for visualization of neurofibromas and schwannomas in NF1 and NF2.
- NF1 shows generalized nerve enlargement with diffuse plexiform neurofibroma, while NF2 shows focal schwannomas of single fascicles in most patients.
- Ultrasound can facilitate further analysis of peripheral nerve tumors in NF1 and NF2 by targeted MRI.

ABSTRACT

Objective: The neurofibromatoses (NF) type 1 and 2 are hereditary tumor predisposition syndromes caused by germline mutations in the NF1 and NF2 tumor suppressor genes. In NF1 and 2, peripheral nerve tumors occur regularly. For further characterizing nerve ultrasound was performed in patients with NF1 and 2.
Methods: Patients with established diagnosis of NF1 (n = 27) and NF2 (n = 10) were included. Ultrasound of peripheral nerves and cervical roots was performed during routine follow-up visits. Healthy volunteers were studied for comparison.
Results: In patients with NF1, median cross-sectional area (CSA) of most nerves was significantly increased compared to controls and to NF2 due to generalized plexiform tumors, which arose out of multiple fascicles in 23 of 27 patients (85%). These were often accompanied by cutaneous or subcutaneous neurofibromas. In NF2, the overall aspect of peripheral nerves consisted of localized schwannomas (80%) and, apart from that, normal nerve segments.
Conclusion: Nerve ultrasound is able to visualize different nerve pathologies in NF1 and NF2. It is a precise and inexpensive screening method for peripheral nerve manifestation in neurofibromatosis and should be considered as the first choice screening imaging modality for all peripheral nerves within reach of non-invasive ultrasound techniques.
Significance: Ultrasound patterns of peripheral nerve pathologies are described for the first time in a large cohort of patients with NF1 and NF2. It is a suitable screening tool and enables targeted MRI analysis.

1. Introduction

Neurofibromatosis (NF) type 1 and 2 belong to the group of autosomal dominant phacomatoses, which are orphan diseases with different prevalence (NF1 1:2500-3000, NF2 1:35000) and

Abbreviations: CSA, cross sectional area; MPNST, malignant peripheral nerve sheath tumor; NCS, nerve conduction study; NF, neurofibromatosis.

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sporadic occurrence in up to 50% (Reynolds et al., 2003; Riccardi, 1981; Salamon et al., 2015; Sperfeld et al., 2002). In both NF types, a gene defect causes down-regulation of tumor suppressor proteins: neurofibromin, encoded on chromosome 17q11.2 in NF1 (Hirbe and Gutmann, 2014) and merlin, also called schwannomin, in NF2 (Sperfeld et al., 2002). NF1 features central and, mostly benign, peripheral nerve tumors next to osseous malformations, cutaneous tumors, axillary or groin freckling, Lisch nodules of the iris, as well as café-au-lait spots (Riccardi, 1981; Sperfeld et al., 2002). In addition, non-neurological tumors such as gastrointestinal stoma tumors or rhabdomyosarcoma as well as cardiovascular involvement and, frequently, neurocognitive deficits occur in NF 1. In NF2, bilateral vestibular schwannomas and tumors of the central nervous system (CNS) are the most characteristic features. With regard to other peripheral manifestations, NF 2 patients frequently develop schwannomas, whereas localized (sub-)cutaneous neurofibromas, diffusely infiltrating cutaneous, subcutaneous, and intramuscular plexiform neurofibroma are typically found in NF1. Furthermore, malignant peripheral nerve sheath tumors (MPNST) develop in 8–13% of NF1 patients (Hirbe and Gutmann, 2014), often arising from plexiform neurofibromas. NF2 patients run a lifetime risk of up to 46% for axonal polyneuropathy (Sperfeld et al., 2002; Bäumer et al., 2013).

Availability of data concerning peripheral nerve imaging in NF patients is limited. In the recent past, MRI-findings of NF1 and NF2 patients were described (Bäumer et al., 2013; Hirbe and Gutmann, 2014; Plotkin et al., 2012); however, the availability of dedicated nerve MRI (MR neurography) is limited to specialized centers, is expensive as a primary screening tool and, in case of young children, additional sedation is necessary.

Nerve ultrasound is a relatively new diagnostic tool with regard to nerve trauma, nerve entrapment and neuropathies (Di Pasquale et al., 2015; Grimm et al., 2015, 2016a,b; Kerasnoudis et al., 2016; Padua et al., 2014; Zaidman et al., 2013). Only few studies have described ultrasound patterns of peripheral nerve tumors (Bodner et al., 2002; Gruber et al., 2007; Karabacak et al., 2014; Loizides et al., 2012; Pedro et al., 2015). In this pilot study, we describe, for the first time, ultrasound patterns of peripheral nerve pathologies in a large cohort of patients with NF1 and NF2.

2. Methods

All patients included in this study, presented to outpatient clinics at Basel or Tübingen University Hospital. Diagnosis of NF1 or NF2 was established according to criteria suggested by the National Institutes of Health (Gutmann et al., 1997; Stumpf et al., 1988). Patients without clinically and/or genetically proven diagnosis of NF1 or NF2 were excluded. Written informed consent was obtained from all patients and controls. B-mode and color coded duplex ultrasound studies of easily accessible peripheral nerves were performed with a high-resolution probe (14–18 MHz broad band linear probes, T7, Mindray company, Darmstadt and Philips Affinity) on one side of the body. Cross-sectional area (CSA) was determined at predefined landmarks (median and ulnar nerve: wrist, middle of forearm, elbow/sulcus ulnaris, mid of upper arm; radial nerve: middle of the upper arm, deep and superficial branch after division; tibial nerve: ankle and poplitea, peroneal nerve: ankle and poplitea, sural nerve at mid-calf, vagal nerve at the carotid sheath and the diameter of the cervical roots C5/6 after leaving transversal process). All nerves were screened for singular tumor manifestations. Maximal tumor/fascicle CSA was measured at these locations. All accessible nerve tumors were screened for malignancy with regard to the following signs: heterogeneity, central necrosis and hemorrhage, ill-defined margins, peritumoral edema, tumor size >5 cm, calcification, rich vascularization, lack of a target sign and intratumoral lobulation (Gruber et al., 2016; Salamon et al., 2015; Lin and Martel, 2001).

3. Statistics

Mann–Whitney-*U*-test was used for evaluating differences concerning epidemiological data (age, gender, height and weight). Mann–Whitney-*U*-test with Bonferroni correction was used to detect differences of nerve CSA between patients and controls. Chi-square-test with Fisher's exact test was used for comparing the frequency of different nerve tumors between NF1 and NF2. For all tests, a two-sided P-value < 0.05 was considered to be statistically significant. For statistical analysis IBM SPSS Statistics, version 22 (Chicago, IL, USA) was used.

4. Results

Between August 2014 and June 2016, 37 patients (27 with NF1 and 10 with NF2) and 28 age-matched controls were included. Baseline characteristics are shown in Table 1.

5. Clinical presentation

Participants were 7 to 60 years of age in NF1 patients and 20–65 years in NF2 patients. 15 patients (56%) with NF1 and 6 patients (60%) with NF2 patients had a non-hereditary disease with a *de novo* mutation.

5.1. NF1

All NF1 patients featured typical skin manifestations such as inguinal and axillary freckling, café-au-lait spots and cutaneous as well as subcutaneous neurofibromas. In four patients, intracerebral tumor manifestations, namely one optic nerve glioma, one optico–hypothalamic glioma and two pilocytic astrocytomas, were identified by MRI studies. Two patients had developed malignant peripheral nerve sheath tumors (MPNST) which were removed prior to study enrollment.

5.2. NF2

Nine NF2 patients (90%) had been diagnosed with bilateral vestibular schwannomas prior to enrollment in our study; the tenth patient was diagnosed with a unilateral vestibular schwannoma. In six patients, multiple intracerebral meningeomas were found. Intraspinal ependymomas had been previously diagnosed in four patients. Five patients had undergone surgery for cosmetic reasons or displacement of neighboring tissue by peripheral nerve tumors. Histopathological examinations and confirmation of schwannoma was obtained in all these cases.

6. Ultrasound results

6.1. NF1

Ultrasound examination of the peripheral nerves showed serpentine-like, partly oval-shaped in length, mostly hypo-echoic, well confined tumors that arose out of multiple fascicles throughout the entire nerve in 23 (85%) patients (Fig. 1, A1 and A2). Color-coded duplex studies revealed poor vascularization of these tumors. CSA values were significantly increased in these cases in most examined nerves (i.e. all studied nerves except the radial nerve) in comparison to the control and NF2 group (all median CSA and p-values are listed in Table 2; Fig. 2). All four remaining NF1 patients showed no visible alteration of the peripheral nerves