Nerve Ultrasound shows Subclinical Peripheral Nerve Involvement in NF2

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Acknowledgements:

We want to thank our lab technicians and residents in clinical neurophysiology for their aid in performing the nerve conduction studies and additional help with ultrasonography.

Number of words in abstract: 145

Number of words in manuscript: 1500

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Running title: HRUS in asymptomatic NF2

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosures: None of the authors has any conflict of interest to disclose.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/mus.25734

ABSTRACT

Title: Nerve Ultrasound shows Subclinical Peripheral Nerve Involvement in NF2

Introduction: Neurofibromatosis type 2 (NF2) is mainly associated with central nervous system (CNS) tumors. Peripheral nerve involvement is described in symptomatic patients, but evidence of subclinical peripheral nerve involvement is scarce.

Methods: We conducted a cross-sectional pilot study in 2 asymptomatic and 3 minimally symptomatic patients with NF2 to detect subclinical peripheral nerve involvement. Patients underwent clinical examination, nerve conduction studies (NCS) and high-resolution ultrasonography (HRUS).

Results: A total of 30 schwannomas was found, divided over 20 nerve segments (33.9% of all investigated nerve segments). All patients had at least one schwannoma. Schwannomas were identified with HRUS in 37% of clinically unaffected nerve segments and 50% of nerve segments with normal NCS findings.

Discussion: HRUS shows frequent subclinical peripheral nerve involvement in NF2. Clinicians should consider peripheral nerve involvement as a cause of weakness and sensory loss in the extremities in patients with this disease.

Keywords: Neurofibromatosis Type 2, Sonography, Peripheral nerve sheath tumors, Asymptomatic, Neuropathy, Subclinical

INTRODUCTION

Neurofibromatosis type 2 (NF2) is a hereditary condition with a prevalence of 1 in 25,000.[1] The occurrence of bilateral vestibular schwannomas is the hallmark of the disease, but numerous other intracranial tumors can develop. Although NF2 is mainly associated with those intracranial tumors, schwannomas can develop in peripheral nerves. Peripheral neuropathy, with or without local nerve compression by a tumor, is reported in up to 66% of patients, though evidence is scarce.[1-3] Subclinical peripheral nerve involvement has also been reported based on nerve conduction studies (NCS), but this information is even more scarce.[3,4] However, this feature may be of importance, as neuropathic complaints could develop in the course of the disease.

High-resolution ultrasound (HRUS) is used increasingly in the analysis of polyneuropathies.[5] Sonographic characteristics of schwannomas have been described.[6-10] We found a large variation in subclinical sonographic peripheral nerve involvement in neurofibromatosis type 1 (NF1).[11] We performed the current study to determine if subclinical peripheral nerve involvement can be observed in NF2 as well.

MATERIALS and METHODS

We conducted a cross-sectional pilot study between January and July 2016 at the Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands, a large general teaching hospital. The Brabant Regional Ethics Committee approved this study (NL54951.028.15) and all patients gave written informed consent. Known NF2 patients without neuropathic complaints were considered for inclusion at our outpatient department. Inclusion criteria were: 1) diagnosis of NF2 based on the Manchester diagnostic criteria,[12] and 2) age >18/<80. Exclusion criteria

were: 1) Comorbidity associated with (poly)neuropathy (e.g. diabetes, alcoholism), and 2) inability to undergo HRUS.

Patients underwent a standardized clinical examination, nerve conduction studies (NCS) and HRUS following a previously published protocol.[11] In summary, one of the investigators (MS) obtained details on clinical history and investigated sensation and muscle strength. NCS of the median, ulnar, fibular, tibial and sural nerves were analyzed by a second investigator (GB). A limited, unilateral protocol was used to limit the burden for participants, but the investigator could choose to measure specific nerves bilaterally. A third investigator (JT) performed bilateral evaluation of the brachial plexus, median, ulnar, fibular, tibial and sural nerves (12 nerve segments total) with HRUS. A Toshiba ultrasound machine (Xario XG; Toshiba, Tokyo, Japan) with a 7-18 MHz linear-array transducer (PLT-1204BT) was used. Nerve cross-sectional area (CSA) was measured at predetermined sites and at sites at which schwannomas were identified. CSA values measured at predetermined sites were compared to previously published reference values.[13] All investigators were blinded to results of the other testing modalities.

RESULTS

Patient Characteristics

Five patients with NF2 were eligible for inclusion: 1 female and 4 males (age 30-66). Though all patients claimed to be asymptomatic upon entering the study, three of them reported mild complaints of sensory loss or weakness in an arm or leg (Patients 1, 2 and 5) during the patient history. We decided not to exclude those patients, as those complaints were vague and not clearly attributable to a specific peripheral nerve, and because NCS and HRUS could

reveal a much wider scope of peripheral nerve involvement than the reported complaints would lead the investigator to suspect.

Clinical examination, NCS and HRUS findings

A total of 59 nerve segments was investigated with clinical examination and HRUS in the 5 patients; 1 nerve segment was not investigated because one patient had a sural nerve graft. Of all nerve segments, 28 were also investigated with NCS.

Clinical examination revealed hypesthesia of the right arm and lateral side of the right lower leg in patient 1, of the lateral side of the left foot in patient 2, and of the lateral side of the lower legs in patient 5. No loss of strength was found. Although symptoms were not clearly attributable to impairment of a specific peripheral nerve, a nerve segment was regarded as clinically affected if an identified area of hypesthesia involved part of the cutaneous region by that particular nerve segment. Therefore 8 nerve segments (13.6%) were regarded as clinically affected in further analysis (1 median, 1 ulnar, 3 fibular, and 3 sural nerves).

NCS showed abnormalities in 4 patients. Detailed results are shown in table e-1. In 2 patients, signs of subclinical carpal tunnel syndrome were found, and 1 patient had absent SNAPs of the sural nerves without other signs of polyneuropathy. Non-specific abnormalities not fitting a mononeuropathy or polyneuropathy were found in 9 nerve segments.

HRUS showed abnormalities in all 5 patients, with 30 abnormal nerve segments (50.8%) total. Detailed findings are shown in table 1. We found 30 schwannomas divided over 20 nerve segments (33.9%). Schwannomas were most often encountered in the median nerve (6/10), followed by the ulnar (5/10), fibular (4/10), and tibial nerves (4/10), brachial plexus (1/10), and sural nerve (0/9). All patients had at least one schwannoma (1-9 schwannomas/patient, size 3-428mm^2). Most schwannomas were hypoechoic, had clearly

defined borders, and showed no vascularization. One patient had 2 'ancient schwannomas', which showed both hypoechoic and hyperechoic regions but no vascularization.

Apart from schwannomas, we found nerve enlargement along the tract of nerve segments. Enlargement was focal; no characteristics of a plexiform neurofibroma or diffuse enlargement were observed. At the focally enlarged sites we frequently observed abnormal, hypoechoic fascicles (Figure 1). In 10 nerve segments (16.9%) we only found focal enlargement without these abnormal fascicles. However, in 3 segments enlargement was only present at entrapment sites, and in 6 enlargement was only mild. One segment (right brachial plexus of patient 1) showed more severe enlargement. Though this enlargement was most likely due to a schwannoma, we were unable to classify it as such with certainty, as the brachial plexus is always hypoechoic on HRUS and we were unable to visualize a clear solitary hypoechoic lesion.

HRUS findings (brachial plexus excluded) were compared to the findings of clinical examination and NCS (Table 2). HRUS showed schwannomas in 37% of the clinically unaffected nerve segments and 50% of the nerve segments with normal NCS findings.

DISCUSSION

Subclinical peripheral nerve involvement in NF2 patients has been reported in NCS and whole-body MRI studies.[2,3] In our study we found multiple sonographic abnormalities in asymptomatic or minimally symptomatic patients. HRUS identified abnormalities more often than NCS, a discrepancy that is also observed frequently in other peripheral nerve diseases.[14]

Sonographic characteristics of schwannomas in our study were comparable to those in previous studies, presenting as solitary round or oval hypoechoic masses with clearly defined

borders and no vascularization.[6,7,9,10] In our study all patients had one or multiple schwannomas. A recent study also found a high incidence of schwannomas on HRUS: in 8 of 10 NF2 patients presenting for routine visits at the outpatient clinic, at least one schwannoma was observed, but the correlation with clinical symptoms was not described.[10] Another recent study found that abnormal, hypoechoic fascicular structure was frequently observed in NF2 patients with neuropathy.[15] The authors did not find schwannomas in their patients, but only median nerves were investigated. In our study, we also frequently observed focal nerve enlargement and hypoechoic fascicles. Although we did not perform a biopsy to obtain a histopathological confirmation, those fascicular lesions are most likely schwannomatous. We did find nerve enlargement without an abnormal fascicular pattern at some sites sites, but this was only very mild or at entrapment sites only, which both are most likely incident findings. Several histopathological studies on peripheral nerves in NF2 showed endoneurial edema, Schwann cell complexes, and proliferations of endoneurial cells,[3,4,16] and an MRI study reported on non-compressive microlesions in nerves that correlated with the severity of the polyneuropathy.[17] Though NF2 is considered to be mostly associated with central nervous system tumors, these findings indicate subclinical peripheral nerve involvement in this disease. Although sensory loss and weakness were previously thought to derive mainly from central nervous system tumors, these findings in peripheral nerves should be taken into account when evaluating NF2 patients with such symptoms.

The current study had several limitations. Only 5 of our patients were eligible for inclusion and several of those reported some non-specific complaints during the history. Nonetheless, all patients had schwannomas of one or multiple clinically unaffected nerves, which confirms that peripheral nerves can be involved in NF2. Our findings and those of several previous studies indicate that this involvement may even be very frequent, but larger studies will be needed to determine the exact scope of subclinical peripheral nerve involvement in NF2.

Also, a limited NCS protocol was used, meaning that subclinical peripheral nerve involvement may be more extensive than that found in this study.

In conclusion, HRUS shows frequent abnormalities of the peripheral nerves, confirming that NF2 is not only a disease with involvement of the central nervous system. Clinicians should consider peripheral nerve involvement as a cause of weakness or sensory loss in the arms and legs in these patients. HRUS appears to be a useful tool to evaluate this, as it is a quick and inexpensive method to investigate multiple nerves. Clinicians should seek anatomically meaningful relationships between abnormalities identified with HRUS and patients' symptoms, as schwannomas may remain asymptomatic, even if they are very large.

ABBREVIATIONS

CSA: Cross-sectional area

HRUS: High-resolution ultrasonography

NCS: Nerve conduction studies

NF1: Neurofibromatosis type 1

NF2: Neurofibromatosis type 2

SNAP: Sensory nerve action potential

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TABLE 1. High resolution ultrasound findings of NF2 patients

	Segments Investigated	Reference Values	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Median R	No. of schwannomas (max CSA)	-	2 (34)	-	3 (46)	1 (166)	2 (15)
	CSA at standard sites (mm ^{2}): Wrist/forearm/arm	11/9/9	**13**/7/9	10/8/**10**	**18**/9/**16**	9/5/**10**	8/4/9
Median L	No. of schwannomas (max CSA)	-	-	-	-	4 (428)	1 (9)
	CSA at standard sites (mm ^{2}): Wrist/forearm/arm	11/9/9	8/5/9	10/6/**10**	**17**/9/**13**	10/9/**15**	6/5/7
Ulnar R	No. of schwannomas (max CSA)	-	1 (89)	-	1 (11)	-	-
	CSA at standard sites (mm ^{2}): Wrist/forearm/distal sulcus/ sulcus/proximal sulcus/arm	7/6/9/ 9/9/9	**9**/**8**/**10**/ **10**/**11**/**15**	7/6/9/ 8/9/5	6/5/7/ **11**/**10**/7	7/5/7/ 6/7/6	3/4/5/ 6/7/5
Ulnar L	No. of schwannomas (max CSA)	-	-	1 (19)	-	2 (10)	2 (19)
	CSA at standard sites (mm ^{2}): Wrist/forearm/distal sulcus/ sulcus/proximal sulcus/arm	7/6/9/ 9/9/9	6/5/5/ **10**/8/8	6/6/6/ 7/**19**/4	5/6/6/ 8/8/9	6/**8**/7/ **10**/6/5	4/5/6/ 7/5/**19**
Plexus R	No. of schwannomas (max CSA)	-	-	-	1 (53)	-	-
	CSA at standard sites (mm ^{2}): Superior/median/inferior trunk	8/8/8	**29**/**24**/**10**	8/5/4	**10**/**10**/-†	5/4/4	4/2/4
Plexus L	No. of schwannomas (max CSA)	-	-	-	-	-	-
	CSA at standard sites (mm ^{2}): Superior/median/inferior trunk	8/8/8	2/5/3	6/6/3	7/6/7	5/5/5	5/5/6
Fibular R	No. of schwannomas (max CSA)	-	2 (185)	-	-	1 (11)	1 (27)
	CSA at standard sites (mm ^{2}): Fibular head/popliteal fossa	11/9	**15**/6	11/8	10/7	**16**/9	**14**/**10**
Fibular L	No. of schwannomas (max CSA)	-	-	-	1 (26)	-	-
	CSA at standard sites (mm ^{2}): Fibular head/popliteal fossa	11/9	9/5	10/**11**	**12**/**13**	**20**/8	11/6

	Segments Investigated	Reference Values	Patient 1*	Patient 2*	Patient 3	Patient 4	Patient 5*
Tibial	No. of schwannomas (max CSA)	-	-	-	-	1 (11)	1 (19)
R	CSA at standard sites (mm^2): Ankle	14	13	13	9	10	13
Tibial	No. of schwannomas (max CSA)	-	-	-	1 (74)	-	1 (92)
L	CSA at standard sites (mm^2): Ankle	14	9	**17**	12	10	12
Sural	CSA at standard sites (mm^2):						
R	Proximal to lateral malleolus	3	3	- ‡	**4**	2	**4**
Sural	CSA at standard sites (mm^2):						
L	Proximal to lateral malleolus	3	3	2	3	1	2
Total segments with abnormalities			5	5	7	6	7
Total segments with schwannomas			3	1	5	5	6

Sites with an increased CSA are shown in bold. The number of schwannomas (CSA of the largest schwannoma) is also shown for each nerve segment. † Not identifiable. ‡ Missing due to sural nerve graft.

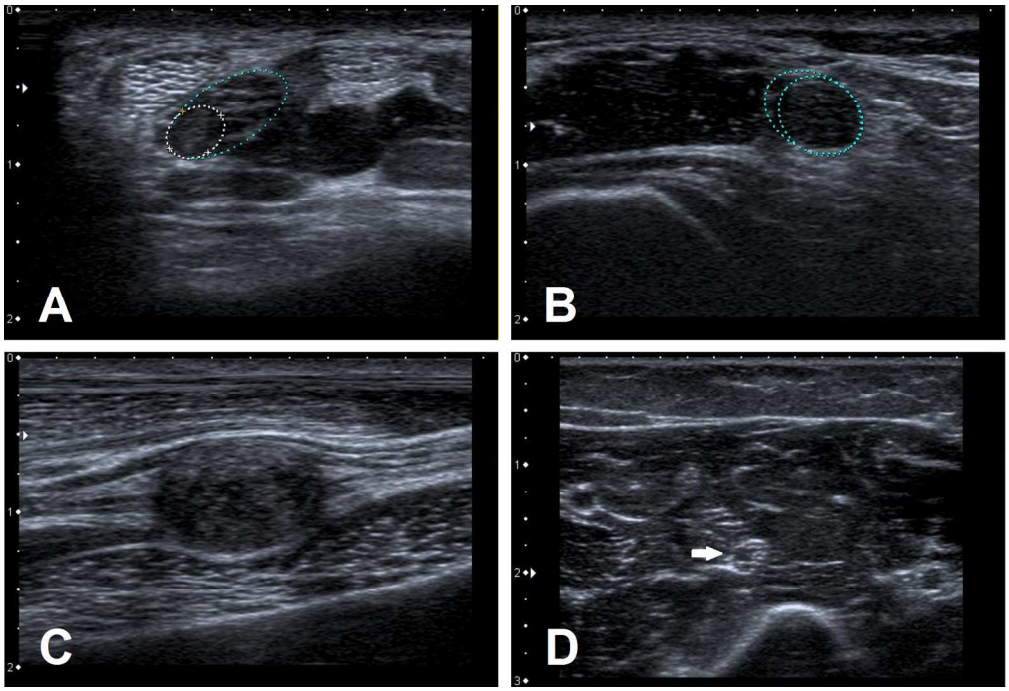
TABLE 2. Correlation of clinically affected nerves, NCS and HRUS

		HRUS (N=49): Number (%)			NCS (N=28): Number (%)	
		Normal	Abnormal	Schwannoma	Normal	Abnormal
Clinically affected	No (N=41)	18 (39%)	23 (56%)	15 (37%)	21 (88%)	3 (12%)
	Yes (N=8)	3 (38%)	5 (62%)	4 (50%)	3 (75%)	1 (25%)
NCS	Normal (N=24)	8 (33%)	16 (66%)	12 (50%)		
	Abnormal (N=4)	2 (50%)	2 (50%)	1 (25%)		

HRUS: high-resolution ultrasonography of the nerves, NCS: nerve conduction studies.

FIGURE LEGENDS

FIGURE 1. Examples of asymptomatic sonographic abnormalities in NF2. A. Schwannoma of the right median nerve in the forearm (Patient 3, CSA 9mm^2), B. Schwannoma of the left fibular nerve in the popliteal fossa (Patient 3, CSA 21mm^2), C. Longitudinal view of a schwannoma of the left median nerve in the forearm (Patient 4), D. Hypoechoic fascicle in the left median nerve in the forearm (white arrow, Patient 5).



Examples of asymptomatic sonographic abnormalities in NF2. A. Schwannoma of the right median nerve at the forearm (Patient 3, CSA 9mm2), B. Schwannoma of the left fibular nerve at the popliteal fossa (Patient 3, CSA 21mm2), C. Longitudinal view of a schwannoma of the left median nerve at the forearm (Patient 4), D. Hypoechoic fascicle in the left median nerve at the forearm (Marked with white arrow, Patient 5).

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