Sequelae following sural nerve biopsy in type 1 diabetic subjects

Short title: Sequele of sural nerve biopsy in type 1 diabetes

Lars B. Dahlin[1], Folke Lithner[4], Lars-Einar Bresäter[5], Niels O.B. Thomsen[1] , Karl-Fredrik Eriksson[2] and Göran Sundkvist[3]†

Department of Clinical Sciences ([1]Hand Surgery, [2]Angiology and [3]Endocrinology), University Hospital Malmö, Malmö, [4]Department of Medicine, Northern Hospital, Umeå and [5]Department of Medicine, Eastern Hospital, Göteborg, Sweden

Correspondence to: Lars B. Dahlin, Department of Clinical Sciences, Hand Surgery, University Hospital, S-205 02 Malmö, Sweden. Phone: +46-40-336769, Fax: +46-40-928855. Lars.Dahlin@med.lu.se

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Abstract

Objectives: To detect postoperative sequelae of sural nerve biopsy. *Material & Methods:* A questionnaire mailed to type 1 diabetic patients (n=24; male/female 23/1; reply n=23) two years after biopsy. *Results:* Type 1 diabetic patients (age 56 [11]; median [IQR]) had a long duration of diabetes (20 [19] years) and all had neuropathy. Three out of 24 patients developed infection (two superficial and one deep) and one had a postoperative bleeding. Less frequent pain among the patients were reported from one center. About one third or more of the patients still complained of pain, mostly mild, in the biopsy area and paraesthesia in the foot two years after surgery. More than two third of the patients were reluctant to a further biopsy; a crucial information in drug trial planning. *Conclusions:* Sequelae of a sural nerve biopsy occur in type 1 diabetes. Risk for wound infections should be considered.

Key words: Diabetes, nerve biopsy, neuropathy, sequelae, sural nerve

Introduction

A sural nerve biopsy can be used to detect and evaluate extent of neuropathy in a variety of conditions (1-4). The procedure is still used to evaluate pathology and biochemical changes in the nerve, even including studies where new drugs against diabetic neuropathy are tested (5-8). It is important to consider the procedure carefully since long lasting postoperative complaints frequently have been described (9, 10). Few differences in complaints has been described between subjects with and without diabetes (DM) or with type 1 and type 2 DM (4, 11, 12), but risks for infections and influence of the surgeon performing the biopsy have not been considered. We describe results of a mailed questionnaire to 24 patients with type 1 DM, in whom a whole sural nerve biopsy was performed (clinical drug trial) at three different centres two years earlier.

Subjects and Methods

Patient material

We performed a whole sural nerve biopsy in 24 patients at three different centres in Sweden as a part of a clinical study evaluating effects of a drug against diabetic neuropathy. Included in the study were patients with insulin dependent type 1 DM and clinical (loss of ankle reflex or diminished sensation in the legs) and electrophysiological signs of polyneuropathy. The biopsies were performed by the same surgeon at each center according to a standardised surgical protocol excising the sural nerve between the lateral malleolus and the Achilles tendon over a length of 5-6 cm (11) at baseline in the drug study. Postoperative regime was identical for all patients: rest during the day of surgery, change of dressing third postoperative day and removal of bandage and sutures 2-3 weeks after the surgery.

Two years after the nerve biopsy a previously evaluated [type 2 diabetic patients and non-diabetic subjects (11)] questionnaire was forwarded to the patients. Reply was received

from 23 of the 24 patients (one woman and 23 men). No biopsy was done as an endpoint procedure in the drug study. The clinical trial, including the postoperative follow up, was approved by the Ethical Committee of Lund University. Due to the Swedish regulations the answers on individual questionnaires have to be unidentifiable, thereby making it impossible to relate a response to a particular individual, including relation to severity of neuropathy.

Results

The 24 patients in the investigated group with type 1 DM had an age of 56 [11] (median [IQR]) years, duration of disease of 20 [19] years and all had polyneuropathy (clinical and electrophysiological signs; inclusion criteria in the study). The results from the questionnaire in 23/24 patients are presented in Table 1. Ten out of the 23 type 1 DM patients experienced discomfort or pain (11/23) in the foot the first day after surgery. All patients, but two, had loss of sensation in the operated foot after surgery (presence of nerve in all biopsies confirmed by microscopy).

Among the patients there was one minor postoperative bleeding, two superficial infections [healed uneventfully with antibiotics (one oral and one intravenously)] and one deep severe infection, which required surgical intervention, and prolonged antibiotic treatment. Three of the patients answered that they could not work as usual after surgery (the one with severe infection on sick leave for 100 days).

At follow-up two years after the biopsy one third of the patients still had pain in the foot. Surprisingly, there was a difference ($p=0.04$; Fisher´s exact test) between the biopsy centres regarding persistence of pain (no patients with persistent pain in Göteborg). Twenty-one of 23 patients still had loss of sensation on the operated foot located around the lateral aspect of the heal (n=9), along the lateral aspect of the foot (n=2), both these areas (n=4) and including the little toe (n=6). Fourteen of 22 patients experienced that the area with loss of

sensation had decreased up to 50% compared to directly after surgery. Cold intolerance in the operated foot was a complaint of 3 out of 23 patients, while allodynia (increased skin sensation when skin touched) was reported by 9 out of 23 patients. One patient described a severe, but transient, “hypersensitivity” in the area of lost sensation, but the problems diminished over time. Paraesthesiae was reported by 13 of 23 patients, mainly with symptoms at rest. Nineteen of 23 patients answered that their complaints generally were mild not requiring painkillers. Sixteen of 23 patients were reluctant to a further biopsy; i.e. would not have the procedure done on the other side if offered.

Discussion

The present results, based on a questionnaire replied by 23 out of 24 type 1 DM patients with neuropathy who underwent a whole sural nerve biopsy as a part of a clinical drug trial, indicate that one third of the patients had persistent symptoms such as pain two years after the biopsy. However, most of the patients described their problems as mild not requiring pain killers, which is in accordance with follow up data after sural nerve biopsies performed on a mixture of healthy subjects and various patients with and without polyneuropathy (3, 4, 12-15).

A sural nerve biopsy is still used (10) in various situations (2747 published articles at PubMed; http://www.ncbi.nlm.nih.gov) : a) clinical trials evaluating drugs against neuropathy (6-8); b) single diagnostic cases (16); c) evaluation of useful additional markers for polyneuropathy (2, 17); d) careful quantification of nerve fibres to assess pathological changes (18) and e) diagnosis in neurological practice (3, 19), although its value has been questioned (9). All our patients were meticulously informed that a second procedure was preferable as an end point in the clinical drug study, but only around one third were positive

to a second biopsy, which is in accordance with our previously published data (11). This is in view of the fact that 19 out of 23 patients reported their problems at the moment as none or mild (3, 4). It emphasises the need for very detailed information even to patients in clinical practice and in clinical trials, particularly considering the high “drop outs” regarding the sural nerve biopsy procedure.

Among our patients we experienced two superficial and one deep infection (latter requiring surgical intervention, intravenously antibiotics and hospital stay), which is an important aspect when considering a sural nerve biopsy in type 1 DM patients (11). In our previous study, also including 21 non-diabetic patients, we did not observe any infections (11). Perry and Bril reported that infections were uncommon after sural nerve biopsy and not more frequently seen among diabetic patients (12). However, infection rates of 12-14% in all types of patients have been reported (3, 19), which is in accordance with our study (12%). A further aspect is the inability to work as usual after surgery, as in three of our patients, and one of them with a sick leave of 100 days. This should be considered in clinical trials since the majority of our type 1 DM patients were active on the labour market.

Generally, there were few differences between the patients from the different centres. Patients only from Göteborg had no persistent pain in the foot at the follow up. We have no explanation for this difference since the procedure at the different centres was identical. It was not related to postoperative infection or bleeding. A weak part of our study is that we did not assess any deficit by a neurological examination. However, that would require that the same person should do such examination of all patients. Therefore, we only sent the previously used questionnaire to the patients making it possible to compare the patients at the various centres. Furthermore, we do not have access to the data from the clinical trial. One may argue

that the patients may have answered the question based on symptoms from their polyneuropathy. However, all patients marked their sensory deficit on the figure indicating that the deficit was related to the sural nerve. Results from question six also indicate that the symptoms were induced by the biopsy and not by neuropathy (similar results from our previous study). Our type 1 DM patients all had signs of polyneuropathy (clinical and electrophysiology) in the lower leg (inclusion criteria in clinical trial), while 40% of previously reported type 2 patients had neuropathy, indicating that presence of polyneuropathy does not increase the risk for postoperative complaints. Interestingly, no differences between our type 1 DM patients and our previously reported type 2 DM patients were generally noted (11) signifying that type 1 DM per se does not increase risk for persistent postoperative complaints after a sural nerve biopsy (12). In almost two third of the type 1 DM patients the area of loss of sensation after the biopsy had diminished during the two year follow-up. This indicates that even in type 1 DM there may be collateral sprouting from neighbouring areas, as previously suggested (4), in spite of presence of neuropathy. Surprisingly, cold intolerance, a common complaint in patients with traumatic nerve injuries in the hand and arm, was a minor problem in our patients.

We conclude that the postoperative complaints of a whole sural nerve biopsy do occur in type 1 DM, and the risk of postoperative infections should be considered. Meticulous information should be provided to patients before undergoing a biopsy whether it is for diagnostic use or as a part of a clinical trial of new therapeutic strategies against neuropathy (9-11). Change of dressing and wound control a few days after surgery is recommended due to risk for deep and superficial infections.

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Table 1. Description of complications and complaints in patients with type 1 diabetes subjected to a whole sural nerve biopsy based on a questionnaire two years after biopsy.

			Number of type 1 DM patients[a)] (n = 24[a)])	Remarks
	Postoperative complications		1	postop bleeding
	Postoperative infections		3	2 superficial and 1 deep infections
1.	Did you have any discomfort			
	(a) during the operation?	Yes	3	
		No	20	
	(b) Directly after the operation?	Yes	10	
		No	10	
		No reply	3	
2.	Did you experience any loss of sensation in the operated area after the operation?	Yes	21	
		No	2	
		No reply	1	
3.	Did you have pain in the operated area during the days after surgery?	Yes	11	
		No	12	
4.	Do you still have pain in the area of operation?	Yes	8	Difference centres: p = **0.04**[b)], no patients with pain in Göteborg
		No	15	
5.	Could you work as usual after surgery?	Yes	20	

		No	3
		Retired	0
6.	Do you have loss of sensation in the operated foot compared to the other foot?	Yes	21
		No	2
7.	Mark the area with sensory deficit in the figure (see Dahlin et al 1997 for figure: I: lateral aspect of heel II: lateral aspect of foot III: lateral aspect of heel and foot IV: lateral aspect of heel and foot, including the little toe).	0	2
		I	9
		II	2
		III	4
		IV	6
		No reply	-
8.	(a) Has the area with loss of sensation decreased compared to the time directly following surgery?	Yes	14
		No	8
		No reply	1
	(b) If yes, how much (%)?	0-25	6
		25-50	5
		50-75	1
		75-100	2
9.	(a) Do you feel pain in the foot?	Yes	7
		No	16
	(b) When?	Day	3
		Night	1
		Day and Night	3
10.	(a) Do you have a problem with cold intolerance in the operated foot/leg?	Yes	3
		No	19
		No reply	1

	(b) If yes, how often?	Often	3
		Seldom	0
11.	(a) Have you experienced problems with increased skin sensation when the skin is touched?	Yes	9
		No	14
	(b) If yes, how often?	Often	4
		Sometimes	5
		Seldom	0
12.	Do you experience discomfort (tingling) along the outside of the foot?	Yes	13
		No	10
13.	If so, when do these symptoms occur?	Rest	7
		Walking	0
		If the area is knocked	8
14.	How would you describe your problems at the moment?	Disturbed sleep	1
		Powerful	1
		Affecting daily living	2
		Mild	14
		None	5
		No reply	-
15.	Do you have to take painkillers often?	Yes	0
		No	23
16.	A theoretical question: would you be prepared to have a surgical biopsy on the other side?	Yes	7
		No	16

[a)] For the questionnaire no reply from one patient. [b)] Chi square test.