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RESEARCH REPORT

Prevalence of Mucopolysaccharidosis Types I, II, and VI in the Pediatric and Adult Population with Carpal Tunnel Syndrome (CTS). Retrospective and Prospective Analysis of Patients Treated for CTS

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Abstract *Background*: We wanted to investigate whether the prevalence of mucopolysaccharidoses (MPS) I, II, and VI was higher than expected in a selected cohort of patients with carpal tunnel syndrome (CTS). CTS is a common finding in patients with MPS, and therefore we screened patients who had undergone surgery for CTS for undiagnosed MPS.

Patients and Methods: Patients who had been operated for CTS were found in databases from two hospitals. Furthermore, patients who had undergone surgery for CTS when under the age of 18 were retrieved from the National Patient Registry. All included patients had a filter paper blood spot sample taken that was subsequently analyzed enzymatically for MPS I, II, and VI.

Results: 425 patients were included. 402 patients tested negative in the first test. 23 had inconclusive result whereof 18 was negative in a second test. The remaining five patients had two inconclusive tests each and were referred for further examination at the Center for Inherited Metabolic Diseases where the diagnosis was excluded. Thus, all included patients were negative for both MPS I, II and VI.

Discussion/Conclusion: Though our sample size is relatively small, results indicate that MPS is not prevalent in a cohort of adult patients with monosymptomatic CTS, and that screening is not indicated in this setting.

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Introduction

Mucopolysaccharidoses (MPS) are a group of inherited diseases caused by deficiencies of lysosomal enzymes, causing progressive accumulation of glycosaminoglycans in the lysosomes and thereby cellular damage. Accumulation develops in all tissues and organs resulting in progressive multiorgan involvement. (Beck et al. 2007) MPS diseases are clinically characterized by a broad phenotypic continuum. Some patients present early with severe manifestations and other later with attenuated symptoms. These latter patients may be difficult to diagnose, partly because their symptoms may be mistaken for signs of more common diseases. MPS is not part of the newborn screening program in most countries including Denmark, and together with the difficult diagnosis this makes the presence of undiagnosed MPS patients in the population probable. Considering this, we investigated whether the prevalence of MPS I, II, and VI is higher than expected in a selected cohort of patients with carpal tunnel syndrome. In Denmark the observed prevalence of all MPS disorders is 6.03 in 1,000,000 inhabitants. The observed prevalence in Denmark of MPS I, MPS II, and MPS VI is 0.74, 0.91, and 0.37 in 1,000,000 inhabitants, respectively (Malm et al. 2008).

CTS is caused by impingement of the median nerve in the carpal tunnel of the wrist. The symptoms include paraesthesia and pain (Katz and Simmons 2002). The symptoms can be reversible when treated sufficiently early with surgical decompression of the median nerve. There is no study that estimates the incidence of CTS in the Danish population. Sweden has a population comparable to the Danish and in 2011 the annual incidence there of CTS in women and men was 428 and 182/100,000 adults, respectively, peaking among women aged 45–54 years (Atroshi et al. 2011). CTS in children and adolescents is rare and often results from trauma. The most common causes of non-traumatic CTS in this age group are mucopolysaccharidoses and mucolipidoses (al-Qattan et al. 1996). CTS is a common symptom in patients with MPS, but diagnosis may be difficult and late because of the limited symptoms being reported by the patients. Previous studies have shown a prevalence of CTS up to 67% in patients with Scheie's syndrome (Thomas et al. 2010), 18% in patients with MPS II (Mendelsohn et al. 2010), and in 6 out of 7 patients with MPS VI (Haddad et al. 1997).

In order to resolve whether focused MPS screening in a selected population with CTS is worthwhile, we decided to screen patients who had had surgery for CTS for MPS.

Patients and Methods

This study was designed with a retrospective and a prospective part. The study was approved by the health research ethics committee (journal number H-2-2011-096) in Copenhagen, Denmark.

In the prospective part, adult patients referred for CTS operation at Nørmark Private Hospital (NPH), Denmark, from 2011 to 2015 were included. If the surgeon found surgical indication at the first consultation, the patient was informed about the project. If the patient consented, they were included in the study, and a filter paper blood sample for MPS testing was taken on the day of the operation.

The patients in the retrospective part already had undergone operation for CTS. One group consisted of patients, who were treated at NPH in the period from 1997 to 2011. A second group consisted of similar patients operated at Køge hospital, Denmark. A third group consisted of patients operated for CTS at an age below 18 years from 2002 to 2012 in Denmark. These patients were retrieved from the National Patient Registry (NPR) using as search criteria the procedure code "decompression of the median nerve."

All patients who met the inclusion and exclusion criteria (had been or was about to be operated for CTS and were below age 60 years when operated) were sent a letter with information and an invitation to participate. If they did not respond, they were either contacted by phone or had a new letter send. If a response was not received after this second approach, no further attempt at contacting the patient was done.

All patients who consented were included and had a filter paper blood spot sample taken. The tests were sent by courier post at room temperature to the Metabolic Laboratory at Hamburg University Medical Center and analyzed enzymatically for activities of α-iduronidase (IDUA), iduronate-2-sulfatase (IDS), and arylsulfatase B (ARSB), the enzymes deficient in mucopolysaccharidosis (MPS) type I, II, and VI, respectively (Cobos et al. 2014).

If the tests had an inconclusive result, a new filter paper blood spot sample was taken. If the test was positive or if the second test was inconclusive, the patient was referred to the Centre for Inherited Metabolic Diseases at Rigshospitalet (RH), Copenhagen for confirmatory testing of MPS I, MPS II, or MPS VI using clinical examination (AML) and determination of urine glucosaminoglycans and leucocyte enzyme activities of the respective enzymes.

Results

In the prospective study, 114 patients were included and in the retrospective 311. All groups had similar demographics apart from the NPR patients who were younger (Table 1).

In the prospective study 115 patients were asked to participate only 1 declined, 78 (68%) of the participants were women and the average age at first test was 47 [20–59].

42% of invited patients from NPH, 30% from Køge Hospital, and 10% from NPR consented to and completed the study (Table 1).

All patients included were negative for all three diseases tested, MPS I, MPS II, and MPS VI. Five patients had two inconclusive tests but all were negative for MPS after further examinations at RH including clinical examination and determination of urine glycosaminoglycans and leucocyte enzyme activities. 95% of the patients had MPS ruled out by the first test (Table 2). In all we did 448 blood spot tests and 28 (6%) were inconclusive. In 19 cases the tests were inconclusive because the activity of arylsulfatase B was below its reference range and could be in agreement with MPS VI, in 4 cases the activity of alpha-iduronidase was below its reference range and could be in agreement with MPS I, in 1 case the activity of iduronate-2-sulfatase was below its reference range and could be in agreement with MPS II, in 3 cases the enzyme activities was in general below their respective reference ranges and in 1 case the activity of both alfa-iduronidase and arylsulfatase B was below their reference ranges probably due to preanalytical problems.

Table 1 Patients invited to participate in the retrospective study ($n = 4,897$)

	Included patients [*n* (%)]						
		Women [*n* (%)]	Average age at first test	Did not want to participate [*n* (%)]	Not possible to contact [*n* (%)]	Not operated for CTS [*n* (%)]	No response [*n* (%)]
Nørmark private hospital	281	227 (81%)	54 [26–73]	139	31	3	216
Køge Sygehus	10	8 (80%)	52 [38–61]	3	0	2	18
National patient registry	20	16 (80%)	25 [19–32]	23	11	40	100
Total	311 (35)			165 (18)	42 (5)	45 (5)	334 (37)

Table 2 Overview of test results

	Total number of included patients: 425		
	1st test negative	2nd test negative	Negative tests at RH
Retrospective study	294	13	4
Prospective study	108	5	1
Total	402	18	5

Discussion and Conclusion

CTS has a high prevalence in the general population, but patients with MPS are affected much more frequently. In this study we examined the clinical utility of screening for MPS I, II, and VI among patients who had undergone surgery for CTS as a high-risk population screening. We screened a total of 425 patients, including 20 who had undergone surgery when under the age of 18. All patients were negative for all tested MPS disorders. As judged by CTS and MPS single Danish prevalence as well as published data on MPS occurrence in patients with CTS and vice versa, we made a rough, overall estimate not to expect a frequency above 0.5% of MPS in patients with CTS. Thus, we had to screen around 800 patients with CTS to be able to find 1–4 patients. We had hoped to include more patients, but it proved difficult to make patients join especially in the retrospective study. It came to our knowledge that many of the patients from the NPR were not operated for CTS. The procedure code "decompression of the median nerve" was also used when patients had undergone surgery for wrist fractures and deep cut injuries in the wrist region among others. Therefore, they could not be included in the study. This probably also explains why 52% of the NPR patients did not respond to our letters. One of the patients from NPR was already diagnosed with MPS and was therefore not included. Furthermore, a number of patients were operated many years ago and may have forgotten about it. The patients were from all over Denmark and some of the patients found it difficult to come to Copenhagen. Some of the patients had the blood sample taken in their own home, but it was not possible in every case. Others may be true monosymptomatic cases, who may find it irrelevant to get tested. Only few patients were below age 18 years, among whom one child was already diagnosed with MPS. This is a weakness of the study in two ways: one is that most MPS disorders would be expected to present in childhood making our cohort less representative, though it should be kept in mind that our aim was to make conclusions about screening for the late onset attenuated forms of MPS; another is that we only found this one case with MPS, when more would be expected as judged from known operations for CTS among Danish MPS children. Thus, our search strategy or Danish national coding practice may be insufficient.

Previously published results on high-risk screening in populations of patients with symptoms compatible with MPS (Table 3) come from seven studies.

In one study they screened two groups of patients (Ly-Pen et al. 2010). One group with CTS under the age of 30 and another group consisting of children and young adults with joint stiffness, flexion contractures, claw hand, trigger fingers, thenar atrophy, poor hand function, and hand paresthesia. From a population of 600,000 they included 12 patients and found low α-L-iduronidase activity compatible with MPS I in the dried blood spot sample in two patients (Haddad et al. 1997).

Nathalie Van Meir and Luc De Smet did a review of 35 articles on pediatric CTS published from 1989 to 2005. They found 163 cases of pediatric CTS and 95 (58%) of the cases were due to MPS. The subtypes were not defined (Van Meir and De Smet 2005). Davis et al. found 13

Table 3 Overview of high-risk studies focusing on symptoms compatible with MPS

	Number of screened persons	MPS	MPS I	MPS II	MPS VI
Lukacs et al. (2014)	–	–	6.1%	3.3%	4.8%
Lukacs (2013)	602	–	8%	5%	4%
Coelho et al. (1997)	9,901	–	8.3%	–	–
Ly-Pen et al. (2010)	12	–	16.7%	–	–
Davis and Vedanarayanan (2014)	13	7.7%	–	–	–
Potulska-Chromik et al. (2014)	11	9.1%	–	–	–
Wang et al. (2006)	58	–	1.7%	–	–

patients with CTS in the age between 2 and 17 years and 1 (7.7%) of them had MPS (Davis and Vedanarayanan 2014). Potulska-Chromik found 1 (9.1%) patient with MPS in 11 children with CTS (Potulska-Chromik et al. 2014).

Wang et al. screened 58 patients under the age of 18 with cardiomyopathy and found one patient with MPS I (1.7%) (Wang et al. 2006).

To conclude, the results of this study cannot support screening for MPS among patients with monosymptomatic CTS, at least in adults though a bigger sample size would have strengthened the conclusion. In young patients with CTS, it cannot be excluded that screening for MPS could be beneficial because of our limited population in this age group. The abovementioned studies may indicate that children with CTS without prior trauma should be tested for MPS, but for a majority of the studies inclusion criteria are vaguely described making the results difficult for clinical use. To diagnose the majority of MPS patients, a more general approach like newborn screening for MPS is probably needed.

Take Home Message

Screening of MPS in adult patients with monosymptomatic CTS is not indicated.

Conflict of Interest

The study was supported by a research grant from Genzyme, Shire, and Biomarin. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

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Informed Consent

All procedures followed were done in accordance with the Helsinki Declaration of 1975 and were approved by the health research ethics committee (journal number H-2-2011-096) in Copenhagen, Denmark. Informed consent was obtained from all participants to be included in the study.

Animal Rights

This article does not contain any studies with animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

MBN was involved in designing the study, contacted the patients, collected, and analyzed the data and drafted the manuscript.

AML was involved in designing the study, gave advice on data collection and analysis and critically revised the manuscript.

NK was involved in contacting the patients and collecting data.

All authors approved the final version of the manuscript.

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