

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence
AUTHORS	Vaeth, Signe; Vaeth, Michael; Andersen, Henning; Chistensen, Rikke; Jensen, Uffe

VERSION 1 – REVIEW

REVIEWER	Bayram Kelle Cukurova University Faculty of Medicine Department of Physical Medicine and Rehabilitation Adana/Turkey
REVIEW RETURNED	02-Jul-2017

GENERAL COMMENTS	This study is a nice study to estimate the prognosis of CMT. But I think it would be more appropriate to know the causes of mortality and the possible additional mortality.
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REVIEWER	Daniel Hackett The University of Sydney, Australia
REVIEW RETURNED	21-Aug-2017

GENERAL COMMENTS	<p>This study provides a good insight into the mortality, prevalence and incidence of CMT in Denmark. The Danish National Patient Registry was used to gather this information with data which was collected between 1977-2012. This study is of great interest and will assist with developing of research questions and studies to improve health and quality of life for people with CMT.</p> <p>Specific comments:</p> <p>Strengths and limitations of this study Second point - change 'form' to 'from' Fourth point – need to place the abbreviation of DNPR after it is first spelt out in the second point Fifth point – try to make this point more concise</p> <p>In figure 1 (flow chart) more information about factors that led to exclusion of patients (e.g. secondary CMT diagnoses n = XX?)</p> <p>Statistical Analysis Page 6, lines 43-49: Please provide clearer information about why patients first diagnosed with CMT registered in DNPR between the years 1977 to 1988 were excluded.</p>
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	<p>Page 7, line 18: SMR – is the ratio of observed to number of death.....? – Please rewrite this sentence. Page 7, lines 20-24: Provide the age and time categories.</p> <p>Results Page 8, line 16 – no need to spell out PPV because it is already done the Statistical Analysis section. Page 9, line 12 – remove extra ‘)’ at end of sentence.</p> <p>Discussion Page 10, line 8 – change 100.000 to 100,000 Page 10, line 10 – ‘The DNPR’ This is sentence is incomplete. Page 10, line 33 ‘the PPV values’??? Remove ‘values’. Page 10, line 55 - ‘Prevalence estimates’ This is sentence is incomplete. Page 10, lines 12-18 – you mention that your study showed similar prevalence rates to Sweden and UK, and then you argue that the other studies had lower prevalence possibly due to searching for undiagnosed relatives with CMT? This section needs to build towards a clearer argument so please rewrite.</p>
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REVIEWER	Stojkovic Tanya G-H Pitié-Salpêtrière Institute of Myology Paris, France
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	<p>The authors report the prevalence and the incidence of Charcot-Marie-Tooth disease in Denmark and the after selecting patients (CMT patients diagnosed in specialized hospital department only), they estimated the standardized mortality ratio and absolute excess mortality ratio.</p> <p>The major concern of the study is the criteria which have been chosen for the diagnosis and inclusion of CMT in this study. Diagnosis of CMT relies on clinical and electrophysiological criteria but genetics is also essential (or at least a family history) to avoid inclusion of others type of neuropathies that are not account in CMT (such as Friedreich disease...). This is essential since as stated by the authors there are many forms of CMT. Some of them (autosomal recessive form, or CMT with respiratory involvement) may have reduced lifespan since they may severely disabled.</p> <p>As stated by the authors, many patients with mild form or even classical form of CMT (ambulant patents) have been probably missed since these patients are not referred to hospital. Thus, the incidence and the prevalence are probably underestimated and this also explain the huge difference in the estimated prevalence between this study and the other ones conducted in Serbia, Norway etc...</p> <p>The highest prevalence in males compared to females is not clearly explained: is there an overrepresentation of CMTX forms? The high mortality observed in young patients (0-29 years) is not clearly explained: is this due to respiratory involvement? Are the authors sure that all these young cases are proven CMT?</p> <p>The mortality has been probably overestimated in this study since many cases are missing.</p>
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	<p>It would be interesting to know if the loss of ambulation and/or respiratory involvement are correlated with higher mortality in CMT patients.</p> <p>At least, knowing that CMT1A is the most common form of CMT, it would be worth investigating to check if this group of patients have higher mortality ratio compared to the general population.</p>
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REVIEWER	<p>Vera Fridman University of Colorado, USA No Competing Interest</p>
REVIEW RETURNED	29-Aug-2017

GENERAL COMMENTS	<p>This study addresses an important question, as there is currently a paucity of research defining mortality in patients with CMT. The study is carefully executed, however, as the authors point out, has several important limitations. CMT encompasses a highly heterogeneous set of diseases, which vary greatly in severity and rate of progression, however individual CMT subtypes are not examined in the study, making the relevance of the findings to individual patients with CMT difficult to determine. As the authors point out, the patient cohort evaluated also likely includes more severely affected individuals who had contact with the hospital system, and may therefore not be representative of CMT patients overall. In addition, no information is provided about the more common causes of death in this cohort. Finally, it should be stressed in the discussion that while the SMR suggests a higher risk of death in the CMT population, the actual increased risk is quite small, as the predicted mortality in the general population is low.</p> <p>Revisions/need for clarification:</p> <ol style="list-style-type: none"> 1. It is not clear what is meant by “hospital contacts”—are the patient admitted to the hospital for care, or are they ambulatory patients coming in for an evaluation without any acute medical concerns? There is reference to the fact that outpatients were added to the registry in 1995—are all prior patients those that were admitted? 2. Who was diagnosing the patients with CMT with the specialized departments? Are diagnoses made by clinicians who are knowledgeable in CMT? Were the patients genetically confirmed to have CMT? 3. What does “misdiagnosed” refer to (page 4, line 50)—are these patients who were not diagnosed? 4. It would be helpful to see a summary table of patient demographics. <p>Minor Points:</p> <ol style="list-style-type: none"> 1. Introduction, first sentence: sensory loss in CMT is mild to severe, not moderate. Select forms are associated with debilitating loss of sensation 2. Page 6, table 2: may be easier to interpret if p-values provided 3. There are no axis labels/legends for figure 2
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VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1

Reviewer Name

Bayram Kelle

Institution and Country

Cukurova University Faculty of Medicine Department of Physical Medicine and Rehabilitation
Adana/Turkey

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

COMMENT: This study is a nice study to estimate the prognosis of CMT.

But I think it would be more appropriate to know the causes of mortality and the possible additional mortality.

RESPONSE: We agree that the cause of mortality is a very important question. We are presently in the process of preparing a study of comorbidities in CMT, to try to find an explanation to the increase in mortality. However, this is a big and laborious project, which is beyond the scope of this study.

REVIEWER: 2

Reviewer Name

Daniel Hackett

Institution and Country

The University of Sydney, Australia

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

General comments:

This study provides a good insight into the mortality, prevalence and incidence of CMT in Denmark. The Danish National Patient Registry was used to gather this information with data which was collected between 1977-2012. This study is of great interest and will assist with developing of research questions and studies to improve health and quality of life for people with CMT.

Specific comments:

Strengths and limitations of this study

Second point - change 'form' to 'from'

RESPONSE: A correction has been made in the revised document.

Fourth point – need to place the abbreviation of DNPR after it is first spelt out in the second point

RESPONSE: A correction has been made in the revised document.

Fifth point – try to make this point more concise

RESPONSE: A correction has been made in the revised document.

In figure 1 (flow chart) more information about factors that led to exclusion of patients (e.g. secondary CMT diagnoses n = XX?)

RESPONSE: A correction has been made in the revised document.

Statistical Analysis

Page 6, lines 43-49: Please provide clearer information about why patients first diagnosed with CMT registered in DNPR between the years 1977 to 1988 were excluded.

RESPONSE: We have expanded the explanation to clarify the reason for exclusion

Page 7, line 18: SMR – is the ratio of observed to number of death.....? – Please rewrite this sentence.

RESPONSE: A sentence has been rewritten to clarify the meaning

Page 7, lines 20-24: Provide the age and time categories.

RESPONSE: A correction has been made in the revised document.

Results

Page 8, line 16 – no need to spell out PPV because it is already done the Statistical Analysis section.

RESPONSE: A correction has been made in the revised document.

Page 9, line 12 – remove extra ‘)’ at end of sentence.

RESPONSE: A correction has been made in the revised document.

Discussion

Page 10, line 8 – change 100.000 to 100,000

RESPONSE: A correction has been made in the revised document.

Page 10, line 10 – ‘The DNPR’ This is sentence is incomplete.

RESPONSE: A correction has been made in the revised document.

Page 10, line 33 ‘the PPV values’??? Remove ‘values’.

RESPONSE: A correction has been made in the revised document.

Page 10, line 55 - 'Prevalence estimates' This sentence is incomplete.

RESPONSE: A correction has been made in the revised document.

Page 10, lines 12-18 – you mention that your study showed similar prevalence rates to Sweden and UK, and then you argue that the other studies had lower prevalence possibly due to searching for undiagnosed relatives with CMT? This section needs to build towards a clearer argument so please rewrite.

RESPONSE: This section has been revised to clarify the argument.

REVIEWER: 3

Reviewer Name
Stojkovic

Institution and Country
G-H Pitié-Salpêtrière
Institute of Myology
Paris, France

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

The authors report the prevalence and the incidence of Charcot-Marie-Tooth disease in Denmark and the after selecting patients (CMT patients diagnosed in specialized hospital department only), they estimated the standardized mortality ratio and absolute excess mortality ratio.

COMMENT: The major concern of the study is the criteria which have been chosen for the diagnosis and inclusion of CMT in this study. Diagnosis of CMT relies on clinical and electrophysiological criteria but genetics is also essential (or at least a family history) to avoid inclusion of others type of neuropathies that are not account in CMT (such as Friedreich disease...). This is essential since as stated by the authors there are many forms of CMT. Some of them (autosomal recessive form, or CMT with respiratory involvement) may have reduced lifespan since they may severely disabled. As stated by the authors, many patients with mild form or even classical form of CMT (ambulant patents) have been probably missed since these patients are not referred to hospital. Thus, the incidence and the prevalence are probably underestimated and this also explain the huge difference in the estimated prevalence between this study and the other ones conducted in Serbia, Norway etc... The highest prevalence in males compared to females is not clearly explained: is there an overrepresentation of CMTX forms?

RESPONSE: In the revised discussion section, we have included a sentence on the aspect of higher prevalence among males. It seems unlikely that the CMTX subtype should explain the difference in prevalence. The most common form of CMTX is caused by mutations in GJB1, which is inherited in an X-linked dominant manner, causing most females carriers to develop a milder CMT phenotype (Siskind et al, 2011). Unfortunately, we do not have the information on CMT subtypes in our data, so this cannot be investigated further.

COMMENT: The high mortality observed in young patients (0-29 years) is not clearly explained: is this due to respiratory involvement?

RESPONSE: The mortality is high relative to the mortality in a comparable group from the general population. In the discussion we explain that the "high mortality" observed in the young patients probably reflects the low mortality in the general population in this age group. The explanation of this issue in the discussion has been expanded.

COMMENT: Are the authors sure that all these young cases are proven CMT?

RESPONSE: The criteria used to identify the young patients are identical to the criteria used for older patients. Our validation study did not indicate a lower predictive value for young patients (Vaeth et al, 2016).

COMMENT: The mortality has been probably overestimated in this study since many cases are missing.

RESPONSE: The mortality is described relative to the general population. The observed number of deaths in the identified group of CMT patients is compared to the expected number of deaths, i.e. the number of deaths that is expected to occur in this group given the same mortality in the CMT patients as the general population. Missing cases will therefore not affect the comparison.

COMMENT: It would be interesting to know if the loss of ambulation and/or respiratory involvement are correlated with higher mortality in CMT patients.

RESPONSE: We agree that it would be very interesting and important to know if loss of ambulation and/or respiratory involvement could be correlated to the higher mortality in CMT cases. We are presently in the process of preparing a study of comorbidities in CMT, to try to find an explanation of the increased mortality. However, this is a large and laborious task, which is beyond the scope of this study.

COMMENT: At least, knowing that CMT1A is the most common form of CMT, it would be worth investigating to check if this group of patients have higher mortality ratio compared to the general population.

RESPONSE: To study the mortality according to CMT subtypes would be very interesting. However, as mentioned in the study, data from the DNPR do not hold information on CMT subtypes, so unfortunately we are unable to investigate this further in the present study.

REVIEWER: 4

Reviewer Name

Vera Fridman

Institution and Country

University of Colorado, USA

Please state any competing interests or state 'None declared':

None

Please leave your comments for the authors below

This study addresses an important question, as there is currently a paucity of research defining mortality in patients with CMT. The study is carefully executed, however, as the authors point out, has several important limitations.

COMMENT: CMT encompasses a highly heterogeneous set of diseases, which vary greatly in severity and rate of progression, however individual CMT subtypes are not examined in the study, making the relevance of the findings to individual patients with CMT difficult to determine.

As the authors point out, the patient cohort evaluated also likely includes more severely affected individuals who had contact with the hospital system, and may therefore not be representative of CMT patients overall.

In addition, no information is provided about the more common causes of death in this cohort.

RESPONSE: We agree that information on cause of death is very important. We are presently in the process of preparing a study on comorbidities in CMT, in which we also plan to gather information on causes of death. However, this is beyond the scope of this study.

COMMENT: Finally, it should be stressed in the discussion that while the SMR suggests a higher risk of death in the CMT population, the actual increased risk is quite small, as the predicted mortality in the general population is low.

RESPONSE: We have expanded the discussion of this point in the revised version

Revisions/need for clarification:

COMMENT 1. It is not clear what is meant by "hospital contacts"—are the patient admitted to the hospital for care, or are they ambulatory patients coming in for an evaluation without any acute medical concerns? There is reference to the fact that outpatients were added to the registry in 1995—are all prior patients those that were admitted?

RESPONSE: All diagnoses registered in the DNPR before 1995 were from hospital contacts where the patient was admitted. This is now dealt with in the discussion.

COMMENT 2. Who was diagnosing the patients with CMT with the specialized departments? Are diagnoses made by clinicians who are knowledgeable in CMT? Were the patients genetically confirmed to have CMT?

RESPONSE: The data from DNPR does not provide exact information on who gave the diagnosis, however, in Danish healthcare this is usually done by a specialist working at one of the specialized departments (neurology, neurophysiology, pediatrics and clinical genetics).

A sentence on this aspect as been added to the discussion in the revised manuscript

COMMENT 3. What does “misdiagnosed” refer to (page 4, line 50)—are these patients who were not diagnosed?

RESPONSE: “Misdiagnosed” refers to a patient with CMT being diagnosed with e.g. another neurological disorder. This is now described in the manuscript.

COMMENT 4. It would be helpful to see a summary table of patient demographics. ‘

RESPONSE: In the text, we give the gender distribution and the average age at first diagnosis for males and females. We find that this is a sufficient description of the patient demographics.

Minor Points:

COMMENT 1. Introduction, first sentence: sensory loss in CMT is mild to severe, not moderate. Select forms are associated with debilitating loss of sensation

RESPONSE: A correction has been made in the revised document.

COMMENT 2. Page 6, table 2: may be easier to interpret if p-values provided

RESPONSE: Table 2 is primarily a descriptive table that shows how the prevalence changes with age for each gender. In the text, we note that the prevalence is lowest in the youngest age group and that the prevalence for males is statistically significant higher than for females. We find that adding p-values for comparison of age categories or comparison of males and females within age categories will complicate the reading of the table, so we prefer the table without p-values.

COMMENT 3. There are no axis labels/legends for figure 2

RESPONSE: We have now added labels on the axes

VERSION 2 – REVIEW

REVIEWER	Daniel Hackett The University of Sydney, Australia
REVIEW RETURNED	18-Sep-2017
GENERAL COMMENTS	You have sufficiently addressed my concerns.