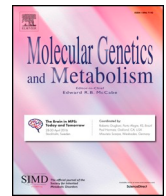




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Evaluation of age of death in Niemann-Pick disease, type C: Utility of disease support group websites to understand natural history

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ABSTRACT

Niemann-Pick disease, type C (NPC) is a neurodegenerative lysosomal storage disease affecting the visceral organs and the central nervous system. The age of initial presentation varies from fetal to adult onset, although childhood onset is most common. The life expectancy for the full spectrum of NPC patients is not well defined, and it is unknown if current supportive care impacts the natural history. In order to assess age of death for a large cohort of NPC patients, we “crowd-sourced” age and year of death from information posted on disease support group website memorial walls. We analyzed data from 338 individuals who died between 1968 and 2018. In addition to age of death, gender can be inferred from given names and photographs. The median age of death was 13 years with a range from 0.1–69 years. Although sex significantly affects survival of NPC1 mutant mice, we did not observe a gender dependent survival difference in NPC patients. Median age of survival across time increased between the earliest patients and the most recently deceased patient; however, we found no significant change in survival over the last 20 years. These data suggest that supportive medical care has not impacted survival in the recent past and provides support for the use of historic controls in evaluating therapeutic interventions.

1. Introduction

Niemann-Pick disease, type C (NPC) is an autosomal recessive, neurodegenerative lysosomal storage disorder that is caused by mutations in either *NPC1* or *NPC2*. The proteins encoded by *NPC1* and *NPC2* are involved in intracellular cholesterol trafficking. Impaired function of either *NPC1* or *NPC2* leads to an endolysosomal accumulation of cholesterol and glycosphingolipids [1]. *NPC1* is an integral membrane protein that facilitates the transport of cholesterol across the endolysosomal membrane, and *NPC2* is a non-enzymatic soluble lysosomal protein that likely transports cholesterol from the lysosomal lumen to *NPC1* [2]. *NPC1* mutations are more common with > 95% of diagnosed individuals having NPC disease due to *NPC1* mutations [3]. NPC is a rare disease with an estimated incidence of approximately 1 in 100,000 live births for the classical disease and potentially higher frequency for late-onset presentations [3,4]. Over 250 pathogenic mutations have been documented in *NPC1* with the most common encoding p.I1061T which has been identified in approximately 15% of disease-associated alleles [5].

The *NPC1* phenotype is very heterogeneous both with respect to age of onset and the specific sign/symptom complex present in each patient [3]. Initial presentation ranges from infantile cholestatic liver disease to progressive neurological disease later in life. Neurological symptoms are progressive and can include progressive developmental delay/school difficulties, cerebellar ataxia, seizures, gelastic cataplexy, vertical supranuclear gaze palsy and dementia. Although age of disease onset is a continuum, NPC patients have been categorized as early-infantile (< 2 years), late-infantile (2- < 6 years), or juvenile (6–15 years) depending on the age of first neurological symptom [6]. Neurological disease progression has been characterized in several cohorts [5–7]. In contrast, available information on lifespan of NPC patients is limited. Given that a number of potential therapeutic agents are being developed [8–11], information on lifespan will be critical to understanding the ultimate efficacy of therapeutic interventions.

We were able to obtain survival data on a large cohort of NPC patients by crowd sourcing public information posted on patient support group websites. Both Fight NPC (www.fightnpc.com) and The National Niemann Pick Disease Foundation (NNPDF; <https://nnpdf.org>) have

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incorporated a memorial webpage on their site. We were able to use these sites to obtain information on date of birth, gender and age of death for 338 individuals with NPC. These data can be used to define lifespan, elucidate effect of gender, and determine if changes in supportive medical care have altered the natural history of NPC. Although there are limitations, crowd-sourced information has the potential of providing critical data regarding the natural history of rare disorders.

2. Materials and methods

Because all individuals are deceased, this work did not require Institutional Review Board oversight. All information is publicly available. On September 28, 2018, we accessed the Fight NPC (http://fightnpc.com/en/memorial_wall) and NNPfD (<https://nnpdf.org/family-services/memorials/>) websites to obtain data on deceased individuals. Duplicate entries were tabulated only once. For each individual we extracted birth date, date of death and inferred gender using photographs and given names. Gender was inferred by three assessors based on agreement of at least two. Individuals were excluded from analysis if the information posted on the website was insufficient to calculate the age at death. Where possible, we cross-checked and confirmed the extracted data with our natural history study database (NCT00344331). Mouse data are from homozygous mutant *Npc1*^{m1N} mice on a BalbC background [12]. Descriptive statistics, median and range, are used in this report. Survival curves are compared using either the log-rank test or log-rank test for trend. The data were graphed and analyzed utilizing Graph Pad Prism 6.0.

3. Results

From the Fight NPC and the NNPfD websites we were able to obtain data corresponding to 338 individuals with NPC. Age at death was calculated based on dates of birth and death. Fig. 1A provides a survival curve for these individuals. Median age of death for this cohort was 13 years. Age of death ranged from 0.1 to 69 years. These data are presented as histograms in Fig. 1B and C. The histograms clearly show a marked increase in deaths starting at 4 years of age. Although the distribution is continuous, the under 30-year-old histogram (Fig. 1C) potentially suggests a bimodal distribution with one group of patients dying in the first decade of life and a second group dying early in the third decade of life.

Multiple research groups have recognized a sex difference in survival between male and female *Npc1* mutant mice as a potential confounder in preclinical evaluation of therapies. Fig. 2A provides data on survival of male and female *Npc1* mutant mice from our research group. Female *Npc1* mutant mice live significantly longer ($p < 0.0001$) than male *Npc1* mice with a median survival of 66 and 78 days for male and female NPC1 mutant mice, respectively. We used our current survival dataset to determine if a similar survival difference was present in male and female NPC1 patients. The male and female survival difference observed in mice was not observed in NPC1 humans (Fig. 2B). Median survival for males and females were 12 and 14 years respectively. The survival curves were not significantly different ($p = 0.31$).

We were also interested in determining if the age of death has changed over time due to advances in available diagnostic methods and medical care. This is critical to know if one is ultimately interested in comparing survival of treated individuals to historical controls. We also evaluated these data by segmenting the dataset into four equal time intervals based on the year of death (Fig. 3A). The first cohort had 4 subjects (1968–1980), second cohort had 37 subjects (1981–1993), third cohort had 163 subjects (1994–2005) and the fourth cohort had 133 subjects (2006–2018). Median ages of death for these four-time intervals were 5, 12, 13, 14 years, respectively. Except for the first time period, where the number of subjects was very low, there did not appear to be a significant increase in survival from 1998 to 2018. The 1968–1980-time interval was excluded from analysis due to the

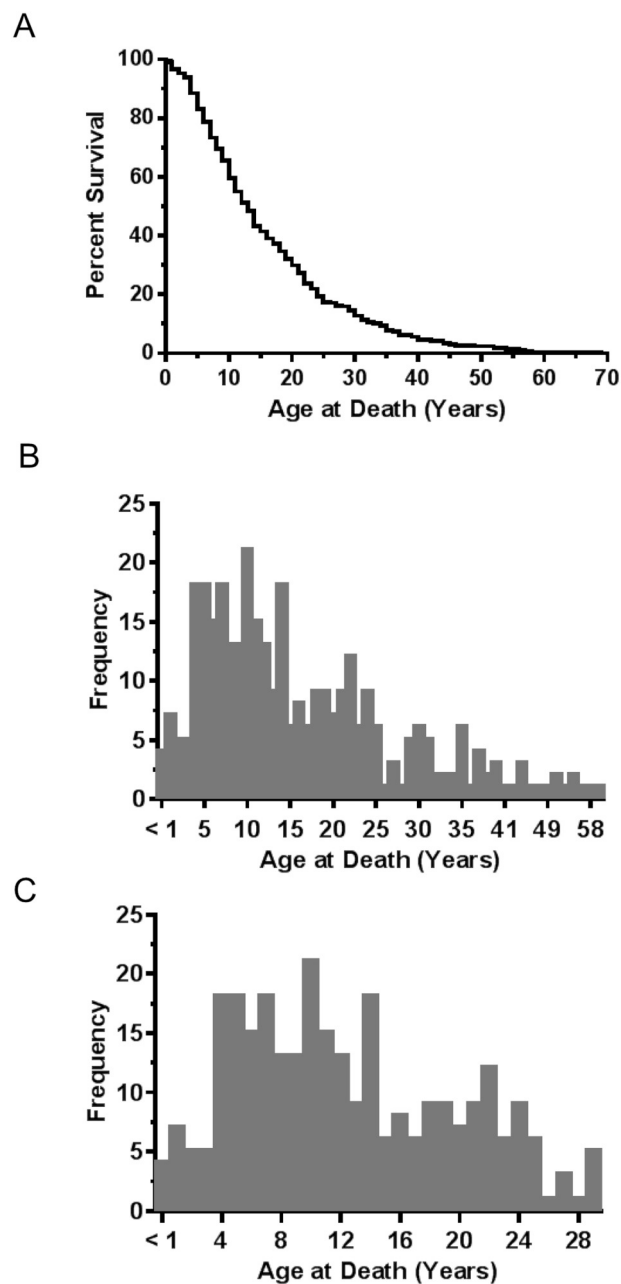


Fig. 1. Age of death. A) Kaplan-Meier survival curve of 338 individuals diagnosed with NPC between 1968 and 2018. Median age of death was 13 years with a range from 0.1–69 years. B) Frequency distribution of age of death for the 338 individuals with NPC. C) Frequency distribution of the 289 individuals who died prior to 30 years of age.

minimal data available. Consistent with our impression, there was no significant trend ($p = 0.12$) for the remaining three survival curves.

NPC1 and *NPC2* were initially identified in 1997 and 2000, respectively [13,14]. The availability of molecular confirmation of an NPC diagnosis may have expanded the phenotypic spectrum of NPC patients. In addition, miglustat was approved by the EMA in 2002 for the treatment of NPC. Although miglustat was not approved by the FDA for NPC, off-label use approaches 40% in our NIH cohort of NPC1 natural history trial participants. To gain insight into whether these two factors impacted NPC lifespan, we analyzed age of death in 5-year intervals over the last two decades (Fig. 3B). The number of subjects in the four groups was 70 (1998–2002), 70 (2003–2007), 54 (2008–2012) and 62 (2013–2018). Median age of death for these time periods were

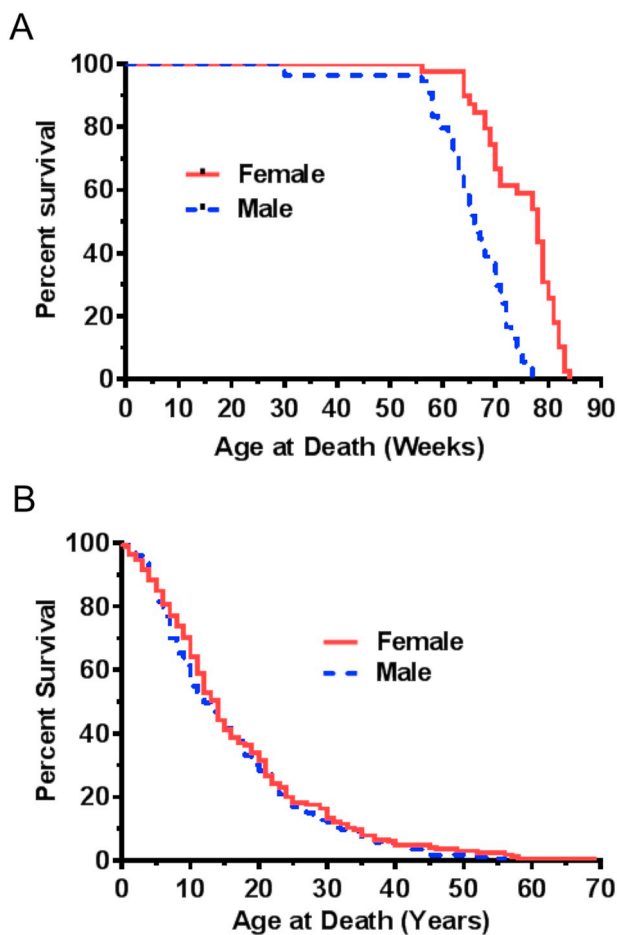


Fig. 2. Effect of gender/sex on the age of death. A) Kaplan-Meier survival curves corresponding to female ($n = 78$, solid line) and male ($n = 66$, dashed line) *Npc1* mutant mice. B) Kaplan-Meier survival curves corresponding to female ($n = 165$, solid line) and male ($n = 173$, dashed line) individuals with NPC.

12, 14, 15 and 14 years, respectively. No significant trend ($p = 0.67$) was observed for the four survival curves.

4. Discussion

Niemann-Pick disease, type C is a lethal neurodegenerative disease resulting in premature death. A number of studies have looked at survival as a function of age of neurological disease onset. Imrie, et al. [6] published a report of 74 patients in a United Kingdom cohort. In the neonatal onset group the mean age of death (\pm SD) was 0.19 ± 0.22 years, in the early-infantile group mean age of death was 5.6 ± 2 years, in the late infantile group the mean age of death was 13.4 ± 6.7 , and in the juvenile onset group the mean age of death was noted to be 25.9 ± 8.9 years. The adolescent/adult group had a mean age of death of 33.7 ± 6.2 years. In a review by Vanier and Millat [1], the typical age of death is reported as a function of the age of onset of neurological symptom onset. Individuals presenting with neurological symptoms evident by the age of 18 months typically died before the age of 5; whereas, individuals with later neurological onset in childhood and adolescence typically died as teenagers with some individuals surviving into their twenties or thirties. Walterfang et al. [15] provided data on the survival of 97 NPC patients stratified by age of neurological onset. Fifty percent of NPC patients with neurological onset either prior to 2 years or between 2 and 11 years of age died within approximately 3 or 7 years of diagnosis. In contrast, 64% of individuals with neurological disease onset after 11 years of age were still alive after 10 years of

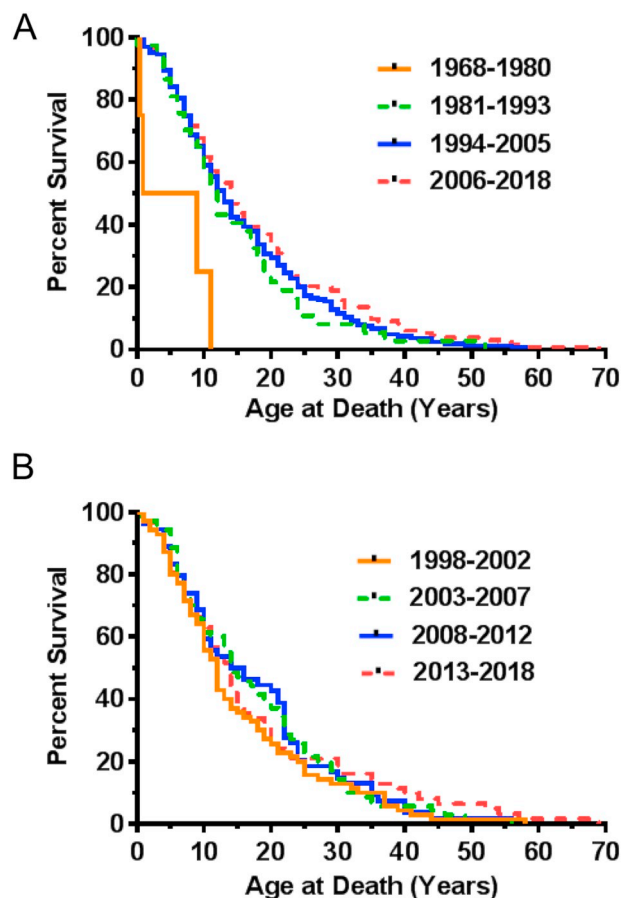


Fig. 3. Effect of year of death on survival curves for individuals with NPC. A) Kaplan-Meier survival curves corresponding to individuals who died in the 11–12 year intervals of 1968–1980 ($n = 4$ orange solid line), 1981–1993 ($n = 37$, green dashed line), 1994–2005 ($n = 163$, blue solid line), 2006–2018 ($n = 133$, red dashed line). B) Kaplan-Meier survival curves corresponding to 256 individuals with NPC who have died in the last 20 years. Each curve represents a 5-year interval. Intervals are 1998–2002 ($n = 70$, orange solid line), 2003–2007 ($n = 70$, green dashed line), 2008–2012 ($n = 54$, blue solid line) and 2013–2018 ($n = 62$, red dashed line).

follow-up. Their data, although limited, also suggest that miglustat might alter the survival time of NPC patients. Jahnova et al. also showed a stability of diagnostic rates and disease manifestations over a 40 year span, with only the adolescent/adult phenotype being ascertained more often in more recent decades [16].

This study reports on the age of death of a cohort of 338 individuals with NPC who died between 1968 and 2018. The median age of death was 13 years with a range from 0.1–69 years. The histograms show an increase in rate of death starting at 4 years of age. This observation argues for early presymptomatic diagnosis by newborn screen [17] and early intervention as potential therapies become available. From this data set, in contrast to what has been observed in mice, we are to conclude that there does not appear to be a significant difference in survival of males and females with NPC. In addition, there does not appear to be a significant difference in lifespan in individuals that have died more recently. This suggests that to date, changes in diagnostic testing and clinical management have not significantly impacted the overall survival of patients with NPC disease. These factors are frequently cited as concerns when historical control groups are used to evaluate therapeutic efficacy.

This study has several limitations. The most significant limitation of this study is that we do not have access to correlating clinical data. Thus, we are unable to stratify this cohort based on age of neurological

onset, age of diagnosis, presence or absence of visceral disease, specific neurological manifestations such as seizures, cause of death or miglustat treatment status. Another limitation is that we cannot independently confirm the diagnosis of NPC or separate case due to mutation of *NPC1* versus *NPC2*. A third limitation is that ascertainment may be biased. We are not able to ascertain the completeness of the dataset and the dataset is clearly biased toward individuals whose guardians are comfortable with the English language and the use of social media. It would be interesting to know if similar datasets are available in other countries and interesting to compare if they show a similar distribution. The dataset is also biased toward individuals who have died more recently. However, even with these limitations, this study still informs our understanding of the natural history of NPC.

To our knowledge, this is the first example of extraction of crowd-sourced mortality data that is not part of a curated patient registry. Other rare diseases such as Pompe disease (<http://www.amda-pompe.org/index.php/main/patients/memorial/>), Batten Disease (<https://bdsra.org/family-profiles/>), leukodystrophies (<https://www.huntshope.org/family-care/wall-of-fame/>), chronic intestinal pseudo-obstruction (<https://www.g-pact.org/memorials/memorial-wall>), or Krabbe disease (<https://krabbeconnect.org/our-heroes/>) have similar memorial walls or member walls in honor of affected children. The available information will vary from site to site; however, as long as the limitations are recognized, the information collected by these sites may complement more traditional sources of natural history data such as formal observational trials, review of case reports and case series, surveys and patient registries.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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