Assessing Amyotrophic Lateral Sclerosis prevalence in Norway from 2009 to 2015 from compulsory nationwide health registers

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Objective: In Norway diagnoses from specialist health care visits, drug prescriptions, and causes of deaths are registered in compulsory health registers. We aimed to determine amyotrophic lateral sclerosis (ALS) prevalence from 2009 to 2015 by combining these registers. **Methods:** We validated the Norwegian Patient Registry (NPR) through hospital files, and linked it with the Norwegian Cause of Death Registry and the Norwegian Prescription Database. Poisson regression models were fitted for estimating gender ratios, time trends and possible interactions. Similar models were used for mortality data subtracted from the dataset. **Results:** Eleven percent of patients with at least one ALS-related entry in NPR did not have ALS. ALS prevalence could nevertheless be reliably estimated through ascertaining cases identified in two separate registers, or with at least two entries in NPR with first entry within four years prior to prevalence date. ALS prevalence remained stable, and was 7.6/100000 (95 % CI 6.9-8.4) at 31st December 2015. Mean male: female ratio was higher for prevalence (1.8; 95% CI 1.6-2.0) than for mortality (1.5; 95% CI 1.2-1.8) ($p=0.04$). There were also significant regional differences in prevalence ($p<0.01$) but not in mortality. **Conclusions:** Norwegian compulsory health registers provide reliable tools for ALS surveillance, and suggest gender and regional differences in survival after diagnosis.

Keywords: amyotrophic lateral sclerosis; motor neuron disease; epidemiology; prevalence

Introduction

Amyotrophic lateral sclerosis (ALS) mortality is increasing within the Norwegian aging population (1). Whereas no nationwide prevalence study has been conducted in Norway, studies based solely on hospital records in two single counties found prevalence rates of 3.67/100,000 on 31st December 1988 (2) and 4.06/100,000 on 31st December 2007 (3).

In Europe, reported ALS prevalence ranges from 1.1/100,000 in former Yugoslavia (4) to 10.3/100,000 in the Netherlands (5). Methods of data collection differ across studies. Combining multiple data sources is generally considered the best strategy (6, 7). Whilst dedicated ALS-register data have the advantage of case ascertainment of high validity, population based prevalence estimates from national compulsory health registers can provide nationwide data in a clinically relevant setting.

Norway has a relatively stable population and equal access to health care. There are public hospitals with neurological services in all counties where ALS patients are diagnosed and typically followed every third month, and medical care including prescription drugs are provided free of charge above a yearly threshold of 237 Euro (8). All drug prescriptions, diagnoses from public and private specialist health care, and causes of deaths are registered in compulsory health registers. The registers have been operating for several years and can be linked through a unique identification number, allowing prevalence estimates of potentially high accuracy (9). The aim of this study was to combine these registers to determine the prevalence of ALS in Norway from 2009 to 2015.

Materials and Methods

Data were extracted from the Norwegian Patient Registry (NPR), the Norwegian Prescription Database (NorPD), the Norwegian Cause of Death Registry (NCoDR) and population data from Statistics Norway in august 2016, and linked through unique person identification numbers. For the purpose of including Norwegian citizens only we excluded individuals without information on residency, and to avoid obvious misdiagnoses we also excluded cases born after 1990.

Norwegian Patient Registry

NPR is an administrative health register for all in –and outpatient admissions to Norwegian hospitals and private practice specialists with public reimbursement. Data on individual patients are available from 1st March 2007. Dates of admission and discharge, diagnoses according to the International Classification of Diseases 10th revision (ICD 10), and surgical/medical procedures are registered electronically for each admission/consultation. We collected data for all entries with ICD 10 = G12.2 from 1st January 2008 to 31st December 2015, including gender, age (10 year birth cohorts), residence (health region), year of first registration, whether the patient was alive on each prevalence day (Statistics Norway), and whether each individual had one single or more entries in the register. Differentiation between

sporadic ALS, familial ALS, and primary lateral sclerosis through a five-digit coding level of G12.2 in ICD10 was not possible until 2017, and was therefore not performed in this study.

Norwegian Prescription Database

NorPD contains a complete electronic listing of all prescription drugs dispensed by Norwegian pharmacies since 2004. Riluzole is only used for ALS, and is offered free of charge to almost all ALS-patients. We collected data on all riluzole dispenses (Anatomical Therapeutic Classification code N07X X02) from 2004 onwards, including gender, age (1 year birth cohorts), year of dispense(s) and year of death (Statistics Norway).

Norwegian Cause of Death Registry

NCoDR collects and processes all death certificates (DCs), and provides digitalized data for the direct, contributing and underlying cause of all deaths in Norway since 1951, from 1996 using ICD 10. We collected data on gender, age at death (1 year bins) and year of death for all those deceased between 31st December 2008 and 31st December 2015 encoded ICD 10 = G12.2 in their DC.

Mortality data for ALS are generally considered reliable (10). In line with this, we have earlier shown that 96 % of deceased patients correctly diagnosed with ALS were retrieved in NCoDR (1).

Hospital files

Hospital files from Akershus University Hospital and Haukeland University Hospital were used to validate ALS diagnoses given at hospitals. Together, these hospitals provide neurological services to approximately 20% of the population in Norway. Two authors (ON and OBT) reviewed the hospital files of all patients registered with ICD10=G12.2 in an outpatient visit or inpatient admission at any department from 1st January 2008 to 31st December 2015. The patient was considered misclassified if not fulfilling the Awaji criteria for possible, probable or definite ALS (11). The identity of all deceased patients identified in this process was sent to NPR to assess the completeness of the registry. We also reviewed hospital files of patients coded as G12.8 and G12.9 (unspecified/other spinal muscular atrophies) to evaluate the specificity of these diagnoses and how often these were reclassified as ALS. Ultimately, to assess whether the diagnostic accuracy in the two university hospitals were representative for the country as a whole, we asked NPR to quantify the number of individuals first coded as G12.8/G12.9 and later as G12.2.

Case definitions and Analyses

For our main prevalence estimates we used the following ALS case definition;

- Alive at prevalence date, minimum one entry in at least two of three registers (riluzole dispense in NorPD, G12.2 in NPR/NCoDR; at least one prior to prevalence date).

or

- Alive at prevalence date, minimum two G12.2 entries in NPR, at least one of these prior to prevalence date, and first entry no more than four years prior to prevalence date.

Prevalence was calculated as the number of patients satisfying our case definition every 31st December from 2009 until 2015, divided by the corresponding total population in Norway. Ninety-five % confidence intervals (CI) for proportions were calculated by the exact method. Poisson regression with robust variance (12) was fitted for prevalence ratios, time trends and possible interactions. Independent variables in the model included gender, age as first and second degree term, prevalence year, and was extended with health regions and interaction terms for regional rate ratios and annual change in national prevalence or gender ratio, respectively. Similar models were fitted for mortality data only, enabling comparison of rate ratios between prevalence and mortality data. Wald test was used to determine whether there were differences in prevalence between health regions, and in addition regional rates were internally standardized by the direct method for comparison. A continuous age variable was constructed by subtracting median birth year from prevalence year, and from this we calculated mean age. A linear regression model with gender, prevalence year, interaction between the two and mean age in the total population was fitted for analyses of mean age trends and differences. We used chi square to test for gender differences in riluzole use. The statistical software Stata (Version 14.2, StataCorp LP, TX, USA) was used for all analyses.

Results

Validation

We first tested the accuracy of ALS diagnoses by reviewing the hospital files at Akershus University Hospital and Haukeland University Hospital for all entries coded G12.2 from 1st January 2008 to 31st December 2015. Out of a total number of 375 patients 42 (11 %) were

misclassified. Of these, only 12 (3 %) were coded with G12.2 twice or more. Misclassified cases generally had diseases with longer expected survival such as congenital motor neuron disease, polyneuropathy and post-polio syndrome. We next tested whether patients diagnosed with G12.2 were retrieved in NPR. Out of a total 277 unique and deceased patients diagnosed with G12.2 at Akershus University Hospital or Haukeland University Hospital from 1st January 2008 to 31st December 2015, 273 (98,6 %) patients were retrieved in the registry. We next reviewed all 70 hospital files from patients coded as G12.8 or G12.9 in the same period. Ten of these fulfilled the Awaji criteria for ALS, and another four later developed ALS. Twelve out of these 14 cases were however coded twice or more as G12.2 during the study period, and therefore not missed in the study. At a country level, a total of 63 individuals initially coded as G12.8 or G12.9 were later coded twice as G12.2 in NPR.

The consistency between register entries are displayed in supplementary Table 1. Because of legal constraints and privacy concerns, direct validation of NorPD is difficult. However, of the 1216 cases with at least two G12.2 entries in NPR (constricted as in the main case definition), 944 (78 %) were retrieved with ever riluzole dispense in NorPD. For NCoDR, the corresponding proportion was 687 out of 971 (71 %).

ALS prevalence

We identified 1720 eligible individuals in NPR from January 1st 2008, 955 in NCoDR from January 1st 2009 and 1556 in NorPD from January 1st 2004. Using the main case definition, ALS prevalence in Norway ranged from 6.9/100,000 (95 % CI 6.2-7.7) on 31st December 2009 to 7.7/100,000 (95 % CI 6.5-7.9) on 31st December 2011 (Figure 1 and Table 1). There were no longitudinal trends (p=0.98). The male: female gender ratio ranged from 1.6 to 2.0 (Table 1), also without any changes throughout the study period. Females tended to be older than males (1.6 years; p=0.14). Longitudinally, mean age increased for females, different from no change among males (p=0.01). Of the 882 male cases identified through either NCoDR or within the NPR main case definition subgroup, 73 % had ever dispensed riluzole. Amongst the 637 females, the corresponding proportion was 68% (p=0.02). Amongst those found in NCoDR, mortality rates were calculated from 2009 to 2015. Within this period, there was no significant trend in mortality rates. The mean male: female ratio was 1.5 (95 % CI 1.2-1.8) for mortality and 1.8 (95 % CI 1.6-2.0) for prevalence (p=0.04).

(Table 1 near here)

Prevalence estimates for possible alternative case definitions are also shown in Figure 1. Using the most conservative definition requiring at least one entry in two separate registers, prevalence ranged from 6.0 (95 % CI 5.4-6.8) to 6.3/100,000 (95 % CI 5.6-7.0). This is most likely an underestimate, as a substantial proportion of patients are either not yet deceased or do not use riluzole, and consequently not registered in NorPD or NCoDR. Using the most liberal case definition allowing for cases only registered once in NPR, estimated prevalence increased by 5.2 % ($p<0.01$) per year and ended at 11.1/100,000 (95 % CI 10.3-12.1). This likely reflects that 11 % of patients reported with G12.2 to NPR did not have ALS, and that these generally live longer than those with ALS and therefore accumulate in the registry over time. Requiring minimum two entries in NPR would reduce this error as only 3 % were misclassified twice, but without further censoring their contribution would also increase over time. In possible agreement with this notion, the prevalence estimate based on this case definition increased by 2.7 % ($p=0.16$) per year and ended at 8.7/100,000 (95 % CI 7.9-9.6).

(Figure 1 near here)

Contribution from different registers

Figure 2 displays how the registers contributed to the prevalence estimates based on our main case definition throughout the study period. As expected, in the first part of the period most patients were registered in both NPR and NCoDR, whereas NorPD became increasingly important at the end of the study. As our latest prevalence date coincided with NCoDRs final recording, no cases could be ascertained from NCoDR at this date. The proportion of cases ascertained exclusively through NPR increased throughout the study period, compensating the declining contribution from NCoDR, and also reducing the proportion of those depending on riluzole dispense.

(Figure 2 near here)

Regional, gender and age distribution

There were significant differences in prevalence between the four health regions ($p<0.01$) (Table 2). A post hoc analysis showed that prevalence rates were 19 % greater in Region West ($p<0.01$) compared to South-East, with 20 % more men ($p=0.07$). Region Middle and North did not differ significantly from South-East with regards to prevalence rates or gender ratio. No geographical differences in rates or gender ratios were seen when analysing mortality data (NCoDR) separately.

(Table 2 near here)

Figure 3 displays age distribution by gender. The age group with highest prevalence amongst both genders was 70-79 years. There were more males than females in every age group. Prevalence dropped amongst the highest age groups in both genders.

(Figure 3 near here)

Discussion

By combining three compulsory health registers, we found a stable prevalence of ALS in Norway from ultimo 2009 to ultimo 2015. The estimated prevalence was almost twice as high as previously reported in single counties (2, 3), with significant regional and gender inequalities. ALS prevalence estimated in other European studies conducted retrospectively display great variability (4-11/100,000) (13-20) . Reports based on European prospective population based ALS-registers are more uniform (7-9/100,000) (21) and concur with our estimates. The difference in ALS prevalence between the present and previous studies exceeds the modest increase in incidence suggested by mortality (1). This discrepancy may be due to methodological differences, as previous studies were based solely on hospital files (2, 3). Although prevalence did not change during our limited observation period, we cannot exclude that also increased survival has contributed to increased prevalence. No disease modifying agent has been introduced in Norway since riluzole in 1996 (22). The use of riluzole did not change during the study period (23). The use of mechanical ventilation amongst ALS-patients is however increasing (24, 25), and has a substantial effect on survival (26). Increased awareness and changes in diagnostic practice, including genetic testing, could also impact prevalence estimates (27). In Norway there seems to be a clustering of familial ALS with the SOD1 H46R mutation (28, 29). These patients generally have long survival (30), and may therefore have substantial impact on prevalence rates despite being relatively few.

The male: female ratio for mortality in our study (1.5) was consistent with that reported previously for incidence rate (1.4) in Europe (31). The gender ratio for prevalence (1.8) was however higher, suggesting that males live longer with the diagnosis. Similar gender differences for ALS survival have been reported previously (32). Independent factors such as young age, spinal onset, the diagnosis of "possible ALS" and symptoms having started more than 12 months prior to diagnosis predict longer survival (32). Of these, we were only able to register age, crudely derived from birth cohorts and prevalence year. Although generally younger males support this coherence, gender differences in adopting therapeutic

measures and life-sustaining interventions such as riluzole, percutaneous gastrostomy, and mechanical ventilation also could influence survival. Indeed, we found that more men than women had dispensed riluzole. Moreover, data from the Norwegian Mechanical Ventilation Register has shown that more men (70%) than women (30%) used long term mechanical ventilation (25). For either of the treatments, our data cannot separate if the observed gender difference is due to patients' or physicians' preferences. It is possible that distinctive gender roles make females more inclined to accept either their own disease course, or to accept the nursing role for their sick spouses (33).

We found differences in ALS prevalence between health regions. Similar geographical differences were not found for mortality. Although the latter analysis was performed post hoc and the discrepancy in regional prevalence versus mortality is uncertain, it may indicate differences in survival. Environmental factors such as smoking and low socioeconomic status have been linked to short survival (34), but we are not aware of such regional differences in Norway. Whereas the use of riluzole seems to be very similar across Norway (23), an earlier report revealed regional differences in adopting long term mechanical ventilation (35). The regional differences in the use of mechanical ventilation did however not correspond to those observed for ALS prevalence, and can therefore not explain these. It should be noted that even small differences in the timing of the diagnostic workup could have substantial impact on prevalence rates, and that the health region with highest ALS prevalence was the first to invent a multidisciplinary ALS team in Norway (36).

There are several pitfalls when using automated hospital discharge and prescription data in epidemiological studies, including errors due to misclassification (37). When evaluating hospital files we found that 11 % of those who were encoded G12.2 once, and 3% of those encoded G12.2 twice, did not have ALS. As these misclassified cases generally had diseases with longer life expectancy than in ALS they would accumulate in NPR over time. Requiring entry in two separate registers would prevent this. However, as a substantial proportion of our patients were either not deceased (increasingly towards the end of our study period), or in line with previous reports had not dispensed riluzole (13, 38), it would underestimate prevalence. To avoid both these pitfalls, we decided that to be included solely based on two or more entries in NPR, the first entry had to be no more than four years prior to prevalence date. This criterion does not allow cases misclassified as ALS to accumulate over time, and thereby restricts the overestimation to approximately 3% throughout the study period. Because the vast majority of ALS patients will meet a specialist more than once and

does not survive beyond four years, it would nevertheless catch most living cases not using riluzole, who would otherwise be lost. Our main case definition therefore included patients either fulfilling this criterion, or registered in two separate registers.

There is a possibility that patients with ALS were not given correct ICD-code (negative misclassification) both in NPR and NCoDR, leading to under ascertainment. From our hospital records, such cases were however very few. It is however possible that we have missed some ALS patients with long survival and rare visits to neurologists, particularly if these do not use riluzole. Some patients with H46R SOD1 mutation might fall into this category (29). Also some ALS patients living in nursing homes could be missed, as severe disability might prevent them from seeing a specialist regularly, and NorPD only collects data from drugs dispensed in pharmacies.

Although each register is compulsory, neither of them was redundant in this study. Because the first prevalence date was set only two years after NPRs first recording, some prevalent cases could have been missed in this registry at this date. NCoDR and NorPD could however catch these cases. NCoDR would obviously gradually lose relevance in recent time, and it is also necessary to combine this registry with other data sources to identify when each case became incident. Although the use of several registers allows verification of the diagnosis and the incidence year, the changing contribution from each register during the study period could potentially disguise a true change in ALS prevalence. Furthermore, the validation of our main case definition relies much on hospital files at two university hospitals. Although neurological services are rather homogenous throughout Norway, we cannot rule out that the diagnostic accuracy at these hospitals do not represent the country as a whole. Our evaluation of reclassified cases however crudely indicates such proportionality.

In conclusion, combining three compulsory health registers in Norway reveals that ALS prevalence remained stable from 2009 to the end of 2015, at a level consistent to other European countries and considerably higher than reported in previous studies based solely on hospital records. Our data also reveal differences in prevalence between genders and regions that are not likely explained by differences in incidence. It is known that males are more likely to use mechanical ventilation, and we here show that males also are more likely to use riluzole. These inequalities need to be further explored.

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Ethical standards

The study was approved by the Regional Committee for Medical and Health Research Ethics (REC South East, ref 2014/1987). The manuscript does not contain clinical studies. The exchange of identities from hospital files to Norwegian Patient Registry was limited to deceased individuals.

Disclosure of interest

The authors report no conflicts of interest.

References

1. Nakken O, Lindstrom JC, Tysnes OB, Holmoy T. Mortality trends of amyotrophic lateral sclerosis in Norway 1951-2014: an age-period-cohort study. Journal of neurology. 2016;263(12):2378-85.
2. Tysnes OB, Vollset SE, Aarli JA. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. Acta neurologica Scandinavica. 1991;83(5):280-5.
3. Gundersen MD, Yaseen R, Midgard R. Incidence and clinical features of amyotrophic lateral sclerosis in More and Romsdal County, Norway. Neuroepidemiology. 2011;37(1):58-63.
4. Alcaz S, Jarebinski M, Pekmezovic T, Stevic-Marinkovic Z, Pavlovic S, Apostolski S. Epidemiological and clinical characteristics of ALS in Belgrade, Yugoslavia. Acta neurologica Scandinavica. 1996;94(4):264-8.
5. Huisman MH, de Jong SW, van Doormaal PT, Weinreich SS, Schelhaas HJ, van der Kooi AJ, et al. Population based epidemiology of amyotrophic lateral sclerosis using capture-recapture methodology. Journal of neurology, neurosurgery, and psychiatry. 2011;82(10):1165-70.
6. Beghi E, Logroscino G, Chio A, Hardiman O, Mitchell D, Swingler R, et al. The epidemiology of ALS and the role of population-based registries. Biochimica et biophysica acta. 2006;1762(11-12):1150-7.
7. Chio A, Logroscino G, Traynor BJ, Collins J, Simeone JC, Goldstein LA, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013;41(2):118-30.
8. Public Health Portal for citizens in Norway. Exemption card for public health services 2017 [Available from: https://helsenorge.no/foreigners-in-norway/exemption-card-for-public-health-services?redirect=false.
9. Simpson S, Jr., Taylor BV. The Scandinavian paradox revisited: Editorial comment on Berg-Hansen et al. 'High prevalence and no latitude gradient of multiple sclerosis in Norway'. Multiple sclerosis (Houndmills, Basingstoke, England). 2014;20(13):1675-7.

Field Code Changed

10. Marin B, Couratier P, Preux PM, Logroscino G. Can mortality data be used to estimate amyotrophic lateral sclerosis incidence? Neuroepidemiology. 2011;36(1):29-38.
11. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology. 2008;119(3):497-503.
12. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC medical research methodology. 2003;3:21.
13. Nygren I, Antonova K, Mattsson P, Askmark H. The ALS/MND prevalence in Sweden estimated by riluzole sales statistics. Acta neurologica Scandinavica. 2005;111(3):180-4.
14. Abhinav K, Stanton B, Johnston C, Hardstaff J, Orrell RW, Howard R, et al. Amyotrophic lateral sclerosis in South-East England: a population-based study. The South-East England register for amyotrophic lateral sclerosis (SEALS Registry). Neuroepidemiology. 2007;29(1-2):44-8.
15. Guidetti D, Bondavalli M, Sabadini R, Marcello N, Vinceti M, Cavalletti S, et al. Epidemiological survey of amyotrophic lateral sclerosis in the province of Reggio Emilia, Italy: influence of environmental exposure to lead. Neuroepidemiology. 1996;15(6):301-12.
16. Huber S, Henn V. Unchanged incidence and prevalence of amyotrophic lateral sclerosis in the canton of Zurich. Schweizer Archiv fur Neurologie und Psychiatrie (Zurich, Switzerland : 1985). 1995;146(2):52-4.
17. Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. Neurology. 2003;60(4):683-9.
18. Cetin H, Rath J, Fuzi J, Reichardt B, Fulop G, Koppi S, et al. Epidemiology of amyotrophic lateral sclerosis and effect of riluzole on disease course. Neuroepidemiology. 2015;44(1):6-15.
19. Pugliatti M, Parish LD, Cossu P, Leoni S, Ticca A, Saddi MV, et al. Amyotrophic lateral sclerosis in Sardinia, insular Italy, 1995-2009. Journal of neurology. 2013;260(2):572-9.
20. Weil C, Zach N, Rishoni S, Shalev V, Chodick G. Epidemiology of Amyotrophic Lateral Sclerosis: A Population-Based Study in Israel. Neuroepidemiology. 2016;47(2):76-81.
21. Hardiman O, Al-Chalabi A, Brayne C, Beghi E, van den Berg LH, Chio A, et al. The changing picture of amyotrophic lateral sclerosis: lessons from European registers. Journal of neurology, neurosurgery, and psychiatry. 2017;88(7):557-63.
22. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. The New England journal of medicine. 1994;330(9):585-91.
23. Norwegian Prescription Database. Startpage Norwegian Prescription Database 2017 [Available from: http://www.reseptregisteret.no/.
24. Tollefsen E, Midgren B, Bakke P, Fondenes O. Amyotrophic lateral sclerosis: gender differences in the use of mechanical ventilation. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2010;17(11):1352-7.
25. Indrekvam S, Fondenes O, Gjerdevik M, Tysnes O-B, Rekand T, Bakke P. Longterm mechanical ventilation in ALS – Outcome and perspective. A 12 year national register study of non-invasive and invasive ventilation in Norway. European Respiratory Journal. 2015;46(suppl 59).
26. Dreyer P, Lorenzen CK, Schou L, Felding M. Survival in ALS with home mechanical ventilation non-invasively and invasively: a 15-year cohort study in west Denmark. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2014;15(1-2):62-7.
27. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Van Damme P, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2012;19(3):360-75.
28. Holmoy T, Braaten O, Hovden IA, Tallaksen CM. [A young woman with a weakening leg]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 2011;131(6):583-6.
29. Ostern R, Fagerheim T, Orstavik K, Holmoy T, Heiberg A, Lund-Petersen I, et al. Hereditary motor neuron disease in a large Norwegian family with a "H46R" substitution in the superoxide dismutase 1 gene. Neuromuscular disorders : NMD. 2012;22(6):511-21.

Field Code Changed

30. Zou ZY, Liu MS, Li XG, Cui LY. H46R SOD1 mutation is consistently associated with a relatively benign form of amyotrophic lateral sclerosis with slow progression. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2016;17(7-8):610-3.
31. Logroscino G, Traynor BJ, Hardiman O, Chio A, Mitchell D, Swingler RJ, et al. Incidence of amyotrophic lateral sclerosis in Europe. Journal of neurology, neurosurgery, and psychiatry. 2010;81(4):385-90.
32. Pupillo E, Messina P, Logroscino G, Beghi E. Long-term survival in amyotrophic lateral sclerosis: a population-based study. Annals of neurology. 2014;75(2):287-97.
33. Bookwala J, Coppola KM, Fagerlin A, Ditto PH, Danks JH, Smucker WD. Gender differences in older adults' preferences for life-sustaining medical treatments and end-of-life values. Death studies. 2001;25(2):127-49.
34. van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. The Lancet. 2017 May 25. doi: 10.1016/S0140-6736(17)31287-4 [Epub ahead of print]
35. Tollefsen E, Gulsvik A, Bakke P, Fondenes O. [Prevalence of home ventilation therapy in Norway]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 2009;129(20):2094-7.
36. Aarli JA, Tysnes OB. [5-year experience with a clinic for amyotrophic lateral sclerosis]. Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke. 1997;117(13):1892-5.
37. Stickler DE, Royer JA, Hardin JW. Validity of hospital discharge data for identifying cases of amyotrophic lateral sclerosis. Muscle & nerve. 2011;44(5):814-6.
38. Kab S, Moisan F, Preux PM, Marin B, Elbaz A. Nationwide incidence of motor neuron disease using the French health insurance information system database. Amyotrophic lateral sclerosis & frontotemporal degeneration. 2017;18(5-6):426-33.