SYMPTOMATIC DRUG THERAPY IMPACT ON AMYOTROPHIC LATERAL SCLEROSIS SURVIVAL

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- Conclusions
INTRODUCTION

Amyotrophic Lateral Sclerosis

- Motor neuron disease
- Average survival: 2-3 years after diagnose
- Incidence: 2 cases out of 100,000
INTRODUCTION

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Cause is still unknown
INTRODUCTION

Amyotrophic Lateral Sclerosis

- Motor neuron disease
- Average survival: 2-3 years after diagnose
- Incidence: 2 cases out of 100,000

Cause is still unknown

There is no effective treatment to slow down, stop or reverse the progression of the disease.
INTRODUCTION

ALS management

**Multidisciplinary approach:**

- **Non-pharmacological therapies**
  - Invasive and non-invasive interventions (dyspnoea)
  - Enteral nutrition by gastrostomy tube (dysphagia)
  - Speech therapy (dysarthria)

- **Pharmacological therapies**
  - Disease-modifying drugs
  - Symptomatic drugs

Figure 1. Clinical manifestations of ALS (Hardiman et al. 2017).
INTRODUCTION

**Disease-modifying therapies**

- **Riluzole**
  Decrease excitotoxicity of MN

- **Edaravone**
  Neuroprotective (antioxidant)

**Symptomatic drug treatments**

- **Antidepressants**
  Depression

- **Anticholinergics**
  Sialorrhea

- **Acetylcysteine and antibiotics**
  Respiratory problems

- **Baclofen**
  Spasticity

- **Nuedexta**
  Pseudobulbar affect
INTRODUCTION

Symptomatic drug treatments

- **Antidepressants**
  - Depression

- **Anticholinergics**
  - Sialorrhea

- **Acetylcysteine and antibiotics**
  - Respiratory problems

- **Baclofen**
  - Spasticity

- **Nuedexta**
  - Pseudobulbar affect

*Figure 1. Clinical manifestations of ALS (Hardiman et al. 2017).*
SYMPTOMATIC DRUG THERAPY
INTRODUCTION

SYMPTOMATIC DRUG THERAPY → ↓ → NUMBER OF HOSPITAL ADMISSIONS
INTRODUCTION

SYMPTOMATIC DRUG THERAPY

↓

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TIME OF HOSPITAL STAYS
INTRODUCTION

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QUALITY OF LIFE
INTRODUCTION

SYMPTOMATIC DRUG THERAPY

↓
NUMBER OF HOSPITAL ADMISSIONS

↓
TIME OF HOSPITAL STAY

↑
QUALITY OF LIFE

? IMPACT ON SURVIVAL
Hypothesis

The early use of medication against ALS symptoms, in addition to symptoms management, could also have an impact on the survival of ALS patients.

Main objective:

Identify the association between early prescription of medication against symptoms of ALS patients and their survival rates.
HYPOTHESIS AND OBJECTIVES

Secondary objectives

- Provide an epidemiological profile of the Swedish MND patients, and a list of most prescribed medications for symptomatic treatment.
- Detect possible deficiencies in data collection and propose different suggestions to improve the quality of the registry.
- Design a suitable statistical study to assess the survival of ALS patients exposed to different medications in early stages of the disease.
- Based on the results of the analysis, hypothesize the underlying mechanisms that can lead to a positive or negative impact on ALS survival.
MATERIALS AND METHODS

The Swedish MND Quality Registry (N = 969)

Stockholm region (N = 388)

Cohort study

Study period: 2015 - April 2019
MATERIALS AND METHODS

- Survival analysis

Outcome → Death / Invasive Ventilation

- Estimated debut
- 3 months after diagnosis
- Exit of study

- Estimated debut
- 3 months after diagnosis
- Exit of study

Underlying time-scale → Time from diagnosis

- End of follow up (2019-04-10)
- Death
- IV

Diagnosis

Exposure to medication
MATERIALS AND METHODS

- Cox proportional hazards regression analysis

Exposure: Medication use until 3 months after diagnosis

- End of follow up (2019-04-10)
- Death
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MATERIALS AND METHODS

- **Cox proportional hazards regression analysis**

  Exposure: Medication use until 3 months after diagnosis

  **Covariates:**
  - Sex (men vs women)
  - Age at diagnosis (continuous variable)
  - Site of symptoms onset (bulbar vs non-bulbar)
  - Diagnostic delay (continuous variable, in months)
  - BMI around diagnosis (continuous variable)
  - ALSFRS-R score around diagnosis (continuous variable)
  - Progression rate (continuous variable)
RESULTS AND DISCUSSION

Sex
- Female
- Male

Diagnose
- ALS
- MND
- PLS
- PSMA

Site of symptoms onset
- Bulbar
- Spinal
- Other
- NA

Age at symptom onset (years)
- 19-45
- 46-55
- 56-65
- 66-75
- 76-90
- NA

Death during the follow-up
- Yes
- No

Cognitive impairment
- No
- Yes – dementia
- Yes – mild cognitive impairment
- NA
RESULTS AND DISCUSSION

- Ever-use of NIV
  - Yes
  - No/unknown

- Ever-use of IV
  - Yes
  - No/unknown

- Ever-use of PEG
  - Yes
  - No – other nutritional interventions
  - No/unknown
RESULTS AND DISCUSSION

- Patients in Swedish MND-quality registry, N=969
  - Patients from Stockholm Region, N=388
    - Patients from regions other than Stockholm Region, N=581
      - Patients with other MND diagnostics, N=62
    - Patients with data incongruences, N=3
  - Confirmed ALS patients, N=326
    - Observations that end on or before enter in Survival Analysis, N=1
  - Validated ALS patients, N=323
    - Patients included in the analysis, N=322
RESULTS AND DISCUSSION

Continuous variables

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR)</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>65.5 (56-71)</td>
<td>322 (100)</td>
</tr>
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<td>Diagnostic delay (months)</td>
<td>12 (8-21)</td>
<td>321 (99.7)</td>
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<tr>
<td>BMI around diagnosis*</td>
<td>23.4 (21.1-26.7)</td>
<td>157 (48.8)</td>
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<tr>
<td>ALSFRS-R score around diagnosis*</td>
<td>38 (33-43)</td>
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More than 50% MV

Problems:

1- Lost of proportionality
2- Wide CI in models that include them
RESULTS AND DISCUSSION

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Sex

- Male 50%
- Female 50%

Site of symptoms onset

- Bulbar 30%
- Spinal 56%
- Other 11%
- NA 3%

More than 50% MV

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RESULTS AND DISCUSSION

Continuous variables | Median (IQR) | N (%) |
--- | --- | --- |
Age at diagnosis (years) | 65.5 (56-71) | 322 (100) |
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Site of symptoms onset

- Bulbar: 30%
- Spinal: 56%
- Other: 11%
- NA: 3%

More than 50% MV

Problems:
1. Lost of proportionality
2. Wide CI in models that include them

Multiple imputation
# RESULTS AND DISCUSSION

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients exposed N (%)</th>
<th>Model 0(^a)</th>
<th>Model 1(^a)</th>
<th>Model 2(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td>42 (13.0%)</td>
<td>1.35 (0.89-2.04)</td>
<td>1.34 (0.89-2.03)</td>
<td>1.28 (0.85-1.94)</td>
</tr>
<tr>
<td><strong>Acetylcysteine</strong></td>
<td>8 (2.5 %)</td>
<td>0.75 (0.19-3.03)</td>
<td>0.74 (0.18-3.00)</td>
<td>0.61 (0.15-2.47)</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>16 (4.9 %)</td>
<td>2.38 (1.28-4.43)*</td>
<td>2.36 (1.26-4.39)*</td>
<td>1.44 (0.75-2.78)</td>
</tr>
<tr>
<td><strong>Baclofen</strong></td>
<td>5 (1.5 %)</td>
<td>0.99 (0.31-3.11)</td>
<td>0.96 (0.30-3.02)</td>
<td>0.93 (0.29-2.92)</td>
</tr>
<tr>
<td><strong>Nuedexta®</strong></td>
<td>15 (4.6 %)</td>
<td>0.88 (0.43-1.80)</td>
<td>0.88 (0.43-1.78)</td>
<td>0.83 (0.40-1.68)</td>
</tr>
<tr>
<td><strong>Riluzole</strong></td>
<td>267 (82.9%)</td>
<td>1.49 (1.00-2.24)*</td>
<td>1.50 (1.00-2.25)*</td>
<td>1.21 (0.87-1.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3(^a)</th>
<th>Model 4(^a)</th>
<th>Model 5(^a)</th>
<th>Model 6(^a)</th>
<th>Model 7(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.05 (0.69-1.58)</td>
<td>1.13 (0.75-1.71)</td>
<td>1.14 (0.75-1.73)</td>
<td>1.19 (0.79-1.82)</td>
<td>1.16 (0.76-1.78)</td>
</tr>
<tr>
<td>0.49 (0.12-2.01)</td>
<td>0.81 (0.20-3.39)</td>
<td>0.84 (0.20-3.48)</td>
<td>0.78 (0.19-3.25)</td>
<td>0.82 (0.20-3.44)</td>
</tr>
<tr>
<td>1.16 (0.60-2.24)</td>
<td>1.14 (0.59-2.20)</td>
<td>1.14 (0.59-2.20)</td>
<td>1.16 (0.59-2.24)</td>
<td>1.12 (0.58-2.17)</td>
</tr>
<tr>
<td>0.89 (0.28-2.86)</td>
<td>0.86 (0.27-2.75)</td>
<td>0.87 (0.27-2.79)</td>
<td>0.85 (0.27-2.71)</td>
<td>0.80 (0.25-2.55)</td>
</tr>
<tr>
<td>0.75 (0.37-1.52)</td>
<td>0.70 (0.34-1.42)</td>
<td>0.69 (0.34-1.41)</td>
<td>0.69 (0.34-1.41)</td>
<td>0.66 (0.32-1.35)</td>
</tr>
<tr>
<td>1.11 (0.74-1.68)</td>
<td>0.97 (0.64-1.46)</td>
<td>0.96 (0.63-1.46)</td>
<td>0.96 (0.64-1.45)</td>
<td>0.82 (0.54-1.28)</td>
</tr>
</tbody>
</table>

*Model: Exposure to medication within three months after diagnosis; Model 1: Adjusted for sex (men vs women); Model 2: Adjusted for sex and site of onset (bulbar vs non-bulbar); Model 3: Adjusted for sex, site of onset and age at diagnosis (continuous variable); Model 4: Adjusted for sex, site of onset, age at diagnosis and diagnostic delay (continuous variable, in months); Model 5: Adjusted for sex, site of onset, age at diagnosis, diagnostic delay and BMI around diagnosis; Model 6: Adjusted for sex, site of onset, age at diagnosis, diagnostic delay, BMI around diagnosis and ALSFRS-R score around diagnosis (continuous variable); Model 7: Adjusted for sex, site of onset, age at diagnosis, diagnostic delay, BMI around diagnosis, ALSFRS-R score around diagnosis and progression rate (continuous variable).

All models are automatically adjusted for time since diagnosis as the underlying time-scale.

*Statistically significant results (p < 0.05)

Assumption of proportional hazards tested using Schoenfeld residuals.
RESULTS AND DISCUSSION

**Model 0**

<table>
<thead>
<tr>
<th>Hazard Ratios (HR)</th>
<th>HR</th>
<th>1.35</th>
<th>2.04</th>
<th>3.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.19</td>
<td>0.75</td>
<td>1.28</td>
<td>2.38</td>
<td>4.43</td>
</tr>
<tr>
<td>0.31</td>
<td>0.99</td>
<td>3.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.43</td>
<td>1.49</td>
<td>2.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.49</td>
<td>2.24</td>
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**Model 7**

<table>
<thead>
<tr>
<th>Hazard Ratios (HR)</th>
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<th>1.16</th>
<th>1.78</th>
<th>3.34</th>
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</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.82</td>
<td>1.12</td>
<td>2.17</td>
<td></td>
</tr>
<tr>
<td>0.58</td>
<td>1.12</td>
<td>2.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td>0.8</td>
<td>2.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.32</td>
<td>0.66</td>
<td>1.35</td>
<td></td>
<td></td>
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<tr>
<td>0.540,82</td>
<td>1.28</td>
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**Antidepressants**

**Acetylcysteine**

**Anticholinergics**

**Baclofen**

**Nuedexta**

**Riluzole**
RESULTS AND DISCUSSION

Underlying mechanism of antibiotics in ALS pathophysiology

Evidences that gut microbiota dysbiosis may have a role in ALS pathogenesis:
RESULTS AND DISCUSSION

Underlying mechanism of antibiotics in ALS pathophysiology

Evidences that gut microbiota dysbiosis may have a role in ALS pathogenesis:

- ALS mice model G3 SOD1
  - ↓ population of butyrate-producer bacteria in gut microbiota. (Fang 2016)
  - Delay of symptoms onset with 2% butyrate water. (Zhang et al. 2017)
RESULTS AND DISCUSSION

Underlying mechanism of antibiotics in ALS pathophysiology

Evidences that gut microbiota dysbiosis may have a role in ALS pathogenesis:

- **ALS mice model G3 SOD1**
  - ▪ ↓ population of butyrate-producer bacteria in gut microbiota. *(Fang 2016)*
  - ▪ Delay of symptoms onset with 2% butyrate water. *(Zhang et al. 2017)*

- **ALS patients**
  - ▪ ↓ population of *Oscillibacter, Anaerostipes, and Lachnospira* in fecal samples. *(Zhang et al. 2018)*
  - ▪ Exposure to antibiotics is a risk factor, especially to beta-lactamase sensitive penicillin. *(Sun et al. 2019)*
Conclusions

Regarding to the Swedish MND Quality Registry:
CONCLUSIONS

Regarding to the Swedish MND Quality Registry:

1. Clinicians and healthcare providers should be encouraged to properly register all the mandatory variables in the Swedish MND quality registry to properly aid future research studies.
CONCLUSIONS

Regarding to the Swedish MND Quality Registry:

1. Clinicians and healthcare providers should be encouraged to properly register all the mandatory variables in the Swedish MND quality registry to properly aid future research studies.

2. A linkage between Swedish MND quality registry and Swedish Prescribed Drug Register should be performed to obtain more accurate information about medication prescribed to ALS patients and, therefore, increase the quality of the registry.
CONCLUSIONS

Regarding to the antibiotics prescription:
CONCLUSIONS

Regarding to the antibiotics prescription:

1. Prescription of antibiotics as symptomatic treatment to avoid respiratory complications may have an impact on ALS patients survival through alteration of gut microbiota population.
CONCLUSIONS

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1. Prescription of antibiotics as symptomatic treatment to avoid respiratory complications may have an impact on ALS patients survival through alteration of gut microbiota population.

2. Antibiotics that target butyrate-producing bacteria (broad-spectrum, gram positive or narrower spectrum ones) may be associated with worse ALS prognosis.
CONCLUSIONS

Regarding to the antibiotics prescription:

1. Prescription of antibiotics as symptomatic treatment to avoid respiratory complications may have an impact on ALS patients survival through alteration of gut microbiota population.

2. Antibiotics that target butyrate-producing bacteria (broad-spectrum, gram positive or narrower spectrum ones) may be associated with worse ALS prognosis.

3. Microbiota-modifying interventions may increase ALS survival by increasing population of butyrate-producing bacteria through prescription of antibiotics, and use of probiotics and prebiotics.
THANK YOU FOR YOUR ATTENTION