Journal Club:
Depression before and after diagnosis with amyotrophic lateral sclerosis

The prevalence of depression among individuals with amyotrophic lateral sclerosis (ALS) is reported to be up to 44%, depending on the assessment methodology. Depression negatively affects quality of life in ALS, and psychological stress is related to poorer survival among individuals with ALS.

This Journal Club article reports on a study from Roos et al. who have calculated the association between ALS and depression, before and after ALS diagnosis. The study provides an elegant example of epidemiologic methods and has important implications for clinical practice, clinical trial design, and public health policy.

HYPOTHESIS AND DESIGN

What is the risk of developing depression following diagnosis with ALS? What is the risk of developing depression before ALS is diagnosed? To answer these important epidemiologic questions, Roos et al. performed a population-based nested case-control study using administrative data from the Swedish national health and population registers. This design also reduces selection bias because cases and controls are sampled from the same parent population that is fully enumerated; all members of the parent cohort need to be examined.

METHODS

Cases. ALS cases were defined as an individual with at least one inpatient or outpatient hospital visit at which ALS was recorded as a diagnosis in the Patient Register, using International Classification of Diseases (ICD) codes (ICD-10 G12.2, ICD-9 335C, ICD-8 348.0, ICD-7 356.1). The first hospital visit for ALS was used as the date of ALS diagnosis. The study included cases that were diagnosed between July 2005 and December 2010.

Controls. For each case, 5 controls who were free of an ALS diagnosis on the date of selection were randomly selected from the study base and were individually matched to the controls on year of birth, sex, and region of residence. This individual matching allows for a more efficient control of these sociodemographic characteristics.

Depression. Depression was ascertained using outpatient ICD codes (ICD-10 F32, F33, F341), and antidepressant use was ascertained from prescription information within the Swedish Prescribed Drug Registers. Users of antidepressants were defined as individuals with ≥2 dispenses of antidepressants.

RESULTS

A total of 1,752 ALS cases and 8,760 controls were included in this study. Depression (either defined as a clinical diagnosis or by antidepressant use) was associated with a higher risk of ALS. Namely, within 1 year after depression diagnosis, there was a 3.6-fold increased risk of ALS (95% CI 2.2–5.8). The risk of ALS decreased as the interval between depression and subsequent ALS increased. Specifically, after more than 3 years following depression diagnosis, the risk of ALS was 0.9 (95% CI 0.6–1.4). A similar pattern was observed for antidepressant use. In examining ALS and the subsequent risk of depression, patients with ALS had a higher risk of depression diagnosis in the year after ALS diagnosis (hazard ratio 6.7, 95% CI 3.9–11.5) that declined in the second year after diagnosis. Further adjustments for education and socioeconomic status (occupation) did not appreciably alter any of the noted effect sizes.

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Roos et al. have brought to attention the risk of depression before and after diagnosis with ALS, and some of the implications of these data:

1. Depression may be a prodromal symptom of ALS.
2. Symptoms of depression may overlap with those of cognitive impairment, leading to potential misclassification of these 2 diagnoses.
3. Depression might be a result of psychological distress experienced by patients with ALS between the first symptom onset and the final diagnosis.
4. Depression may be a reaction to the ALS diagnosis.
5. This study may have importance for clinical trial design. Stress and depression may affect study enrollment. Although this has not been examined specifically in an ALS population, ALS depression could factor into enrollment success and retention in clinical trials.

**Strengths of this study.** There are several strengths of this study related to its study design and research question:

1. This is the largest study regarding number of cases of ALS depression (before and after diagnosis) to date.
2. The cases come from a defined and completely enumerated population allowing control selection to be completely random and thus free from selection bias.
3. Data were collected prospectively and therefore free from recall bias.
4. The exposure and outcome data are collected independently and uniformly for the entire population, thus avoiding biases inherent in pulling information from different sources.
5. An important strength of this study is the ascertainment of cases of ALS using hospital discharge data. Bias could result if the diagnostic accuracy of ALS was low. A study of 2,650 cases in the Danish National Patient Register showed a high validity of ICD codes for capturing ALS diagnoses. While slight bias toward the null could occur with a small number of incorrectly identified cases, bias away from the null would only occur if the misidentification of cases was strongly related to the exposure of interest—which would likely not be the case here since the case identification procedures were blind to exposure status.
6. Another important strength of this study is the ascertainment of depression using both a clinical diagnosis and antidepressant dispenses (≥2).

**Study limitations.** Weaknesses of the study are as follows:

1. There were a limited number of confounding factors examined in this study. As is generally an issue with the use of administrative data, limited clinical information was available. For example:
   a. A potential confounder is frontotemporal dementia, especially for ALS associated with C9ORF72 expansion mutations. C9 mutations can lead to psychiatric symptoms years before presentation of ALS or frank frontotemporal dementia.
   b. Other factors not examined in the present study are pain and head trauma, each of which is associated with both depression and ALS.
   c. They did not capture cigarette smoking. Although the evidence is not completely consistent, there is some evidence for smoking as a risk factor for ALS. To assess whether confounding by cigarette smoking may be occurring using administrative data, other outcomes could be used either as proxies for smoking or for use in a negative control outcome approach, as is done in other studies using registry data.
   d. This study did not differentiate familial from sporadic ALS. It is possible that some exposures may not affect risk of ALS among subjects with a familial form of ALS. However, familial forms of ALS only account for 5% to 10% of all ALS cases.
2. There were no data before start of the different registries. The absence of data from before a given registry started could lead to exposure misclassification to the extent that a study subject was exposed (e.g., took antidepressants) before the start of the registry. However, any such exposure misclassification would be expected to be nondifferential and therefore, if anything, bias true associations toward the null.

Despite these concerns, is the calculated risk relevant to current neurologic practice? Indeed, the most consistently established nongenetic risk factors for ALS are age and male sex, and both were accounted for in this study. This, in combination with the other major strengths of this study, make this an important contribution to ALS epidemiology and ALS clinical practice.

**AUTHOR CONTRIBUTIONS**

Dr. Cragg: drafting/revising the manuscript, interpretation of data. Dr. Seals: drafting/revising the manuscript, interpretation of data. Dr. Cashman: drafting/revising the manuscript, interpretation of data. Dr. Weisskopf: drafting/revising the manuscript, interpretation of data.

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DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES
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