

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark

In "Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark," Papp et al. reported that using the 2015 International Panel for NMO Diagnosis (IPND) criteria, the prevalence of NMO spectrum disorder (NMOSD) in Denmark in persons older than 16 years is 1.09 per 100,000 persons. They noted that this rate is higher than that reported in previous studies in Australia/New Zealand (0.7) and Catalonia (0.89) and lower than that reported in previous studies in Region of Southern Denmark (4.4) and Olmsted County, Minnesota (3.9). Asgari and Flanagan, who authored the articles from Region of Southern Denmark and Olmsted County, respectively, believe that Papp et al.'s calculation of the prevalence of NMOSD is low because of the (1) exclusion of 16 patients who were seropositive for aquaporin-4 IgG, (2) use of aquaporin-4 IgG data from multiple rather than a single laboratory, some of which used a less sensitive assay, and (3) use of only 2 (rather than all) of the core clinical criteria for NMOSD. Papp et al. respond that (1) their findings actually fall within Flanagan et al.'s wide interquartile range (0.8–7.1) and that (2) the 2015 IPND criteria emphasize exclusion of alternative diagnoses and all excluded seropositive cases were inconsistent with NMOSD due to weak positivity, features consistent with MS, good response to disease-modifying therapy, or long-term stability without treatment. It is clear that estimates of NMOSD prevalence vary depending on the criteria used to define NMOSD and the study population. Nonetheless, it seems to consistently be less than 5 per 100,000 persons in the regions studied.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2019;93:722. doi:10.1212/WNL.00000000000008323

Reader response: Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark

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We thank Papp et al.¹ for calling attention to neuromyelitis optica spectrum disorder (NMOSD) epidemiology. They reported lower NMOSD prevalence than previous studies.^{2,3} They explained the higher Olmsted County (United States) prevalence by statistical random chance,¹ but failed to mention its almost 100% population coverage and the seroprevalence design (testing aquaporin-4 [AQP4]-IgG in >80% with CNS demyelinating disease), which markedly improved capture compared with their much larger population of 4.5 million. Similar prevalence was observed in a population-based study from Denmark (1998–2008),² possibly reflecting a specific diagnostic algorithm with the incidence rate based on a diagnosis of NMOSD within the study period in contrast to disease onset; subsequently, myelin oligodendrocyte glycoprotein IgG was detected in some seronegative patients.⁴ Papp et al.¹ used information from tertiary hospitals and laboratory databases, used only 2—rather than all—of the core clinical criteria, included some older-generation (less sensitive) assays, and excluded AQP4-IgG–seropositive patients who became seronegative on retesting, which is well recognized in NMOSD after immunotherapy treatment, despite its recognized specificity of >99%.

Author disclosures are available upon request (journal@neurology.org).

Finally, they excluded 98.3% of cases by review of records alone without confirmation with questionnaire, interview, clinical examination, or MRI. Overall, we suspect that these limitations led to underestimation of NMOSD frequency.

1. Papp V, Illes Z, Magyari M, et al. Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark. *Neurology* 2018;91:e2265–e2275.
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Author response: Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark

Viktoria Papp (Odense, Denmark), Zsolt Illes (Odense, Denmark), Melinda Magyari (Copenhagen), Nils Koch-Henriksen (Aarhus, Denmark), Jette Lautrup Frederiksen (Glostrup, Denmark), Finn Sellebjerg (Copenhagen), Egon Stenager (Odense, Denmark), and Thor Petersen (Aarhus, Denmark) *Neurology*® 2019;93:723. doi:10.1212/WNL.0000000000008324

The authors¹ agree that Flanagan et al.² may have achieved a more complete coverage of patients with neuromyelitis optica spectrum disorder, but identified a very low number of patients. Therefore, their confidence intervals (CIs) are wide, and they do overlap with our prevalence data (Flanagan et al.: 3.9/100,000 [95% CI: 0.8–7.1] vs Papp et al.¹: 1.09/100,000 [95% CI: 0.81–1.44]), in contrast to Asgari et al.³ (4.4/100,000 [95% CI: 3.1–5.7]). Our prevalence data were consistent among the Danish regions.¹

Asgari et al.³ reported remarkably higher incidence as well, which could not be confirmed by our¹ and the other Danish study.⁴

Most patients with suspected multiple sclerosis (MS) were routinely tested for anti-AQP4; therefore, the high frequency of negative tests explains the rejection rate. All the excluded seropositive cases had weak positivity at a single time point or by inaccurate assay accompanied by several red flags: clinical and radiologic features strongly suggesting MS; good response to disease-modifying therapy (DMT); and long-term stability without treatment. Assessing the staining pattern by semiquantitative cell-based assay is highly dependent on experience and crucial in cases with weak/uncertain positivity. Seroconversion occurred spontaneously or during DMT (see supplementary data).¹ The 2015 International Panel for Neuromyelitis Optica Diagnosis criteria emphasized the importance of excluding alternative diagnosis.⁵

We believe that our results—based on a large population in our nationwide study, different data sources, and blinded and anonymous reevaluation of cases by a board of experts (clinical and laboratory data plus MRIs)—provide an accurate estimate of NMOSD in Denmark.

1. Papp V, Illes Z, Magyari M, et al. Nationwide prevalence and incidence study of neuromyelitis optica spectrum disorder in Denmark. *Neurology* 2018;91:e2265–e2275.
2. Flanagan EP, Cabre P, Weinschenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol* 2016;79:775–783.
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Editors' note: Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke

In “Ordinal vs dichotomous analyses of modified Rankin Scale (mRS), 5-year outcome, and cost of stroke,” Ganesh et al. reported that the ordinal mRS correlates better with 5-year mortality/disability/cost of care than the dichotomized mRS (using either 0–1 or 0–2 to measure good outcome). To optimize the utility of future stroke trials, these findings should be considered when determining how to compare poststroke mRS scores. One problem the authors noted with dichotomization is that patients with premorbid disability are likely to automatically be characterized as having a poor outcome because they cannot get better than their premorbid status poststroke. On a related note, Bruno comments that determining the prestroke mRS is subjective and that there are no guidelines for doing so. He recommends abandoning the use of the mRS to assess prestroke functional status and, instead, using a simple dichotomization of all patients as able or unable to complete activities of daily living prestroke. Ganesh et al. agree that there is a need for prestroke disability to be uniformly designated, but they caution that their poststroke disability data suggest that an ordinal approach may be higher yield than a dichotomized one. Notably, although Ganesh et al. demonstrate that the ordinal mRS correlates with 5-year mortality/disability/cost of care, the scale has been criticized for its dependence on the ability or inability to walk resulting in the automatic classification of all patients who are unable to walk, regardless of their cognitive status, as an mRS score 4 or 5.

Ariane Lewis, MD, and Steven Galetta, MD
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Reader response: Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke

Askiel Bruno (Augusta, GA)
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This important observation about the frequently reported prestroke modified Rankin Scale (mRS)¹ is worthy of consideration. The mRS was not designed for use before brain injury.^{2,3} Scoring the mRS categories 0–2 requires a comparison between prestroke and poststroke functional states, which is not possible prestroke. Consequently, there are no guidelines to score a prestroke mRS, making it a rather subjective measure. One recent study reported a modest correlation between a prestroke mRS and other markers of function,⁴ but the exact method of scoring the prestroke mRS is not stated. The mRS scores 3–5 can be scored without comparison to prestroke functional status based primarily on the ability to walk without assistance (mRS ≤3) and the ability to get out of bed (mRS ≤4), but this is likely of limited value.

Because prestroke functional assessment is important, as pointed out by Ganesh et al.,¹ it behooves us to establish a defined and valid method of doing so. The mRS is not suited for this purpose. In the interest of avoiding potentially detrimental delays during acute stroke evaluation, 1 simple validated question may be very useful: “Before this stroke, did the patient require help from another person for everyday activities?”⁵

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Author response: Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke

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We thank Dr. Bruno for the comment on our article.¹ Although our focus was on how the ordinal and dichotomous forms of the 3-month modified Rankin Scale (mRS) relate to long-term outcomes and costs, we did exclude patients with prestroke mRS >1 and >2 to verify our findings in additional analyses. We agree that there is a need to establish more uniform methods for ascertainment of prestroke disability, which currently relies on measures like the mRS that were not originally designed for this purpose and may be vulnerable to confounding factors, such as sex differences in premorbid mRS ratings.² The single-question approach suggested by Dr. Bruno is likely to be useful in time-pressured clinical situations to establish whether a patient has significant premorbid disability. However, it does not quantify prestroke disability, which is important for evaluating treatment outcome (i.e., to what extent did the patient's poststroke disability differ from their prestroke disability). As demonstrated in another recent analysis from the Oxford Vascular Study,³ each increment of additional poststroke disability (per the mRS) in patients with prestroke disability is associated with worse mortality and institutionalization rates and higher health care costs.

1. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM; Oxford Vascular Study. Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. *Neurology* 2018;91:e1951–e1960.
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CORRECTION

Minor hallucinations in Parkinson disease

A subtle symptom with major clinical implications

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In the article "Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications" by Lenka et al.,¹ Dr. Kulisevsky's last name was misspelled. The authors regret the error.

Reference

1. Lenka A, Pagonabarraga J, Pal PK, Bejr-Kasem H, Kulisevsky J. Minor hallucinations in Parkinson disease: a subtle symptom with major clinical implications. *Neurology* 2019;93:259–266.

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Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications

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