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# Changes in the Nijmegen Questionnaire in severe asthma patients treated with dupilumab

## Cambios en el Cuestionario de Nijmegen en pacientes con asma grave que reciben dupilumab

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## Abstract

**Objective:** To assess changes in Nijmegen Questionnaire (NQ) scores in patients with severe asthma treated with dupilumab and their relationship with disease control.

**Methods:** A retrospective study was conducted in patients with severe asthma treated with dupilumab. Epidemiological and clinical data were collected, as well as results of questionnaires: NQ, asthma control test (ACT) and Asthma Quality of Life Questionnaire (AQLQ), assessing the changes after one year of treatment.

**Results:** A total of 18 patients were included, 12 males, with a median age of 54 years and a range between 27 and 67 years old. The median result of the NQ at the start of dupilumab was 15.5 points (1-34) and at 12 months was 7 points (0-35). Before treatment, five patients (27.77%) had a NQ greater than 23 points compatible with hyperventilation syndrome (HVS). The median ACT score was 19 (10-24) and at the 12-month control it was 23 (12-25). The median AQLQ was 5 points (3-7) at the start of dupilumab and 6.08 points (3.50-7) after 12 months of dupilumab. This study observed changes in NQ scores after 12 months of dupilumab treatment, irrespective of initial NQ scores.

**Conclusions:** Incorporating the NQ into the assessment of biologic response in severe asthma may provide additional insights into patient monitoring. Proper management of comorbidities, including HVS, is essential for optimizing asthma outcomes, as uncontrolled comorbidities can confound asthma control.

**Keywords:** Nijmegen questionnaire; Asthma quality of life questionnaire; Severe asthma; Dupilumab; Hyperventilation syndrome.

## Resumen

**Objetivo:** Evaluar los cambios en las puntuaciones del Cuestionario de Nijmegen (CN) en pacientes con asma grave que reciben dupilumab y su relación con el control de la enfermedad.

**Métodos:** Estudio retrospectivo llevado a cabo en pacientes con asma grave, tratados con dupilumab. Se recopilaron datos epidemiológicos y clínicos, así como los resultados de los cuestionarios CN, Test de Control del Asma (TCA) y Cuestionario de Calidad de Vida en Asma (AQLQ), evaluando los cambios tras un año de tratamiento.

**Resultados:** Se incluyeron 18 pacientes (12 hombres y 6 mujeres), con mediana de edad de 54 años (rango: 27-67 años). La mediana del CN al inicio del tratamiento con dupilumab fue de 15.5 puntos (rango: 1-34) y a los 12 meses de 7 puntos (rango: 0-35). Antes del tratamiento, 5 (27.77%) pacientes reportaron una puntuación superior a 23 puntos del CN, compatible con síndrome de hiperventilación (SHV). La mediana de la puntuación ACT fue de 19 (10-24) y en el control a los 12 meses fue de 23 (12-25). La mediana de la puntuación AQLQ fue de 5 puntos (3-7) al inicio del tratamiento con dupilumab y de 6.08 puntos (3.50-7) luego de 12 meses de tratamiento. Se informaron cambios en las puntuaciones NQ después de 12 meses de tratamiento con dupilumab, independientemente de las puntuaciones iniciales del cuestionario.

**Conclusión:** La incorporación del Cuestionario de Nijmegen en la evaluación de la respuesta al tratamiento con biológicos en pacientes con asma grave puede proporcionar información adicional para su seguimiento. El tratamiento adecuado de las comorbilidades, incluido el síndrome de hiperventilación (SHV), es decisivo para optimizar los desenlaces en el control del asma.

**Palabras clave:** Cuestionario de nijmegen; Cuestionario de calidad de vida en asma; Asma grave; Dupilumab; Síndrome de hiperventilación.

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## INTRODUCTION

Dysfunctional breathing refers to a group of chronic respiratory pattern disorders that result in respiratory and non-respiratory symptoms such as dyspnea, chest pain, dizziness, and fatigue.[1,2] Among the various patterns described, the most frequently reported is hyperventilation syndrome (HVS). The Nijmegen Questionnaire (NQ) is a validated tool for distinguishing patients with and without HVS by assessing three dimensions: shortness of breath, peripheral tetany, and central tetany. The NQ comprises 16 questions, scored on a scale from 0 ("never") to 4 ("always"), with a score of ≥23 required for a diagnosis of HVS. The NQ demonstrates a sensitivity of 91% and specificity of 95% in detecting HVS.[4]

The prevalence of HVS is challenging to establish but is estimated to affect 6–10% of the general population and 29% of asthmatic patients.[5] Discriminating between HVS and asthma using the NQ can be complex, as several items in the questionnaire may overlap with asthma manifestations.[3] While the NQ has been validated in mild-to-moderate asthma, its reliability in patients with severe asthma remains unexplored.[6] This study aimed to assess changes in NQ scores in patients with severe asthma treated with dupilumab and their relationship with disease control.

## METHODS

A retrospective study was conducted involving patients aged ≥ 18 years with a diagnosis of severe asthma and on treatment with dupilumab. Clinical and demographic data, along with results from the NQ, Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), and changes in forced expiratory volume in 1 second (FEV1) from spirometry (measured in milliliters and percentage), were collected from electronic medical records. All variables were measured at baseline and after 12 months of treatment. The ethics committee of Hospital Universitario La Paz approved the study (PI-5027).

## RESULTS

Eighteen patients (12 males) with a median age of 54 years (range: 27–67) were included. **Table 1** presents asthma phenotypes and associated comorbidities per patient.

The median NQ score decreased from 15.5 (range: 1–34) at baseline to 7 (range: 0–35) after 12 months. Similarly, the median ACT score improved from 19 (range: 10–24) to 23 (range: 12–25), and the median AQLQ score increased from 5 (range: 3–7) to 6.08 (range: 3.50–7). At baseline, the median FEV1 was 3005 mL (p25-p75: 2318-3253) 81% (p25-p75: 71%-87%), improving to 3160 mL (p25-p75: 2755-3775) 87% (p25-p75: 78-97%) after 12 months of treatment. Changes by patient are described in **Table 1**.

Five patients (27.8%) had baseline NQ scores ≥ 23, consistent with HVS. Four of these patients were women, three of whom had anxiety diagnoses, while one had severe vocal cord dysfunction.

Although no significant minimum difference has been established to consider changes in NQ, after 12 months of dupilumab treatment, 13/18 patients showed a decrease in NQ scores, including 3/5 patients with baseline scores ≥ 23, whose scores dropped below the HVS diagnostic threshold.

## DISCUSSION

The use of the Nijmegen questionnaire in the follow-up of patients with severe asthma is an available tool in addition to other classic questionnaires used to monitor asthma control, such as the ACT or the AQLQ. Although its development focused on differentiating between patients with and without HVS, it can be a useful tool in the follow-up of asthma, as it offers a broad view of the symptoms associated with dysfunctional breathing patterns. It assesses the patient's perception of these symptoms and can help us personalize patient management and integrating non-pharmacological interventions such as respiratory retraining or cognitive-behavioral therapy.

One of the main criticisms of the NQ is that it can overestimate the frequency of HVS in asthmatic patients since symptoms assessed in the questionnaire are compatible with asthma, so control of the disease can normalize the results of NQ.

To test this hypothesis, the results of the ACT score were collected. In our 13 patients with improvement in NQ, all patients also reflected improvement in ACT but from the remaining 5 patients with no improvement in NQ, interestingly 4/5 had improved in ACT. Therefore, it does not seem that there is always an established relationship between improvement in asthma control and improvement in NQ, the presence of dysfunctional breathing patterns and asthma can coexist in the same patient.

In relation to the 5 patients with HVS, despite all presented improvement in ACT, two patients maintain high scores in NQ compatible with HVS, which shows that HSV can persist despite maintaining good asthma control in some patient.

In these patients where asthma control is observed but respiratory symptoms persist, follow-up with NQ is especially useful, as it can help address the hypothesis that the lack of respiratory symptom control is related to other comorbidities.

These findings highlight the importance of exploring different domains of response to biological treatments. NQ may serve as a valuable monitoring tool in asthma, identifying HVS comorbidity and providing insight into the patient's perceived disease control. Thomas et al.[7] suggested using the NQ as a continuous variable to assess the cognitive and perceptual burden of disease rather than as a binary diagnostic tool for HVS.

To assess improvement in asthma control, in addition to the ACT, changes in quality of life through the AQLQ and changes in objective measures such as spirometry were assessed. The median FEV1 increased by 155 mL (6%), and the AQLQ score improved by 1.08 points. Patients with baseline NQ scores ≥23 demonstrated notable improvements, Changes by patient are described in **Table 1**.

When respiratory symptom control is not satisfactory in patients with severe asthma being treated with biological

**Table 1**. Clinical characteristics and changes in questionnaires and FEV1.

| Nº | Asthma phenotype | Comorbidities | NQ previous | NQ after | ACT previous | ACT after | AQLQ previous | AQLQ after | FEV1 previous | FEV1 after |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Mixed | Nasal polyposis | 15 | 7 | 20 | 23 | 6.06 | 5.34 | 2420 (87%) | 2550 (92%) |
| 2 | Eosinophilic | GERD<br>Bronchiectasis<br>Nasal polyposis | 21 | 5 | 23 | 25 | 5.78 | 6.46 | 3740 (108%) | 4200 (118%) |
| 3 | Mixed | Bronchiectasis<br>Nasal polyposis | 2 | 1 | 18 | 23 | 3.75 | 6.70 | 3390 (72%) | 4050 (87%) |
| 4 | Eosinophilic | Nasal polyposis | 10 | 4 | 17 | 22 | 5.25 | 6.40 | 3870 (99%) | 3780 (98%) |
| 5 | Eosinophilic | Bronchiectasis<br>Obesity<br>Nasal polyposis | 3 | 9 | 24 | 21 | 6.40 | 6.25 | 3170 (77%) | 3070 (75%) |
| 6 | Mixed | GERD<br>Nasal polyposis | 21 | 13 | 19 | 25 | 5.10 | 6.70 | 2000 (56%) | 2740 (78%) |
| 7 | Mixed | Bronchiectasis<br>GERD<br>Nasal polyposis | 16 | 3 | 23 | 25 | 6.50 | 6.00 | 3070 (81%) | 3400 (90%) |
| 8 | Eosinophilic | GERD<br>Nasal polyposis | 13 | 22 | 13 | 17 | 4.59 | 4.28 | 3040 (82%) | 2900 (79%) |
| 9 | Mixed | Nasal polyposis | 2 | 3 | 11 | 20 | 4.00 | 7.00 | 2890 (67%) | 4000 (87%) |
| 10 | Mixed | GERD<br>Obesity | 5 | 4 | 21 | 23 | 5.00 | 5.40 | 2060 (60%) | 2570 (69%) |
| 11 | Allergic | Bronchiectasis | 8 | 5 | 13 | 23 | 5.00 | 6.00 | 1500 (71%) | 1310 (63%) |

*...continuation table 1.*

| Nº | Asthma phenotype | Comorbidities | NQ previous | NQ after | ACT previous | ACT after | AQLQ previous | AQLQ after | FEV1 previous | FEV1 after |
|---|---|---|---|---|---|---|---|---|---|---|
| 12 | Mixed | Obesity<br>Nasal polyposis | 1 | 5 | 24 | 25 | 7.00 | 7.00 | 2970 (66%) | 3250 (73%) |
| 13 | Mixed | GERD<br>Nasal polyposis | 22 | 0 | 20 | 25 | 4.00 | 7.00 | 3130 (85%) | 2860 (79%) |
| 14 | Eosinophilic | Anxiety<br>GERD<br>Nasal polyposis | 33 | 16 | 21 | 24 | 5.00 | 5.44 | 2040 (86%) | 3760 (120%) |
| 15 | Mixed | GERD<br>Nasal polyposis | 25 | 11 | 15 | 21 | 4.90 | 6.15 | 4990 (106%) | 5180 (116%) |
| 16 | Eosinophilic | Anxiety<br>Nasal polyposis | 27 | 7 | 15 | 19 | 4.03 | 5.70 | 3280 (81%) | 2800 (86%) |
| 17 | Mixed | Anxiety | 34 | 25 | 16 | 20 | 4.80 | 5.50 | 2290 (80%) | 3510 (100%) |
| 18 | Allergic | Vocal cord dysfunction | 32 | 35 | 10 | 12 | 3.00 | 3.50 | 2400 (87%) | 2320 (87%) |

ACT: asthma control test; AQLQ: Asthma Quality of Life Questionnaire; F: female; FEV1: Forced expiratory volume; GERD: gastroesophageal reflux disease; M: male; NQ: Nijmegen questionnaire.

therapies and improvement has been observed in both spirometry and quality of life, before considering that the treatment is ineffective or insufficient, assessing alterations in dysfunctional respiratory patterns can be useful, as it may be the key to identifying the inconsistency found between apparently good clinical control but a poor perception of the disease.

Proper management of comorbidities, including HVS, is essential for optimizing asthma outcomes, as uncontrolled comorbidities can confound asthma control.[8] Managing HVS with respiratory physiotherapy has been shown to improve quality of life and symptom perception in daily activities and exercise.[9]

As limitations, this study is retrospective and has a small sample of patients, moreover, it does not have a formal statistical study, the intention of the study is to describe the changes observed in the sample, not to extrapolate the data to the general population. Therefore, larger studies are needed to assess the usefulness of NQ in patients with severe asthma. To our knowledge, this is the first study to evaluate changes in NQ scores in severe asthma patients treated with dupilumab or other biological therapy.

# CONCLUSION

In our sample of patients with severe asthma treated with dupilumab, changes in the NQ were observed. We believe this questionnaire may be useful as an additional tool for severe asthma management, as it can provide data on dysfunctional breathing patterns that may be confused with therapeutic failure and can be solved by personalizing management with non-pharmacological measures.

# DECLARATIONS

## Author contribution's

All authors contributed to the study conception. All authors extracted data for the purposes of this submission. The first draft and manuscript were written by Isamar De Agrela Mendes and all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

## Financial sources statement

The authors declare that no funding was received for the present study

## Conflicts of interest

Isamar De Agrela Mendes, Jorge Correa Borit, Valentin Lopez Carrasco, Mihaela Carmen Ifrim, Carlos Turiel Gómez, Leticia De Las Vecillas and Santiago Quirce have no conflicts of interest to declare. Javier Dominguez Ortega has received in the last 3 years financial compensation for advisory meetings and/or conferences from ALK, GSK, Gebro, Sanofi, Teva, AstraZeneca, Novartis, LetiPharma, Chiesi, Cipla and Bial.

## Ethics responsibilities

The study was carried out in adherence to ethical standards, the Regulation of the General Health Law on Health Research, and the Declaration of Helsinki.

## Human and animal rights and informed

Consent This article does not contain any studies with human, or animal subjects performed by any of the authors.

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## Permissions

All figures and tables are original.

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