CNS Demyelinating Attacks Requiring Ventilatory Support With Myelin Oligodendrocyte Glycoprotein or Aquaporin-4 Antibodies

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Abstract

Background and Objective

Severe attacks of myelin oligodendrocyte glycoprotein (MOG) antibody–associated disorder (MOGAD) and aquaporin-4 (AQP4) antibody–positive neuromyelitis optica spectrum disorder (AQP4-NMOSD) may require ventilatory support, but data on episodes are limited, particularly for MOGAD. We sought to compare the frequency, characteristics, and outcomes of MOGAD and AQP4-NMOSD attacks requiring ventilatory support.

Methods

This retrospective descriptive study identified Mayo Clinic patients (January 1, 1996–December 1, 2020) with MOGAD or AQP4-NMOSD and an attack requiring noninvasive or invasive ventilation at Mayo Clinic or an outside facility by searching for relevant terms in their electronic medical record. Inclusion criteria were (1) attack-related requirement for noninvasive (bilevel positive airway pressure or continuous positive airway pressure) or invasive respiratory support (mechanical ventilation); (2) MOG or AQP4 antibody positivity with fulfillment of MOGAD and AQP4-NMOSD clinical diagnostic criteria, respectively; and (3) sufficient clinical details. We collected data on demographics, comorbid conditions, indication for and duration of respiratory support, MRI findings, treatments, and outcomes. The races of those with attacks requiring respiratory support were compared to those without such attacks in MOGAD and AQP4-NMOSD.

Results

Attacks requiring ventilatory support were similarly rare in patients with MOGAD (8 of 279, 2.9%) and AQP4-NMOSD (11 of 503 [2.2%]) \((p = 0.63)\). The age at attack (median years [range]) (MOGAD 31.5 [5–47] vs AQP4-NMOSD 43 [14–65]; \(p = 0.01\)) and percentage of female sex (MOGAD 5 of 8 [38%] vs AQP4-NMOSD 10 of 11 [91%]; \(p = 0.04\)) differed. The reasons for ventilation differed between MOGAD (inability to protect airway from seizure, encephalitis or encephalomyelitis with attacks of acute disseminated encephalomyelitis 5 [62.5%] or unilateral cortical encephalitis 3 [37.5%]) and AQP4-NMOSD (inability to protect airway from cervical myelitis 9 [82%], rhombencephalitis 1 [9%], or combinations of both 1 [9%]). Median ventilation duration for MOGAD was 2 days (range 1–7 days) vs 19 days (range 6–330 days) for AQP4-NMOSD (\(p = 0.01\)). All patients with MOGAD recovered, but 2 of 11 (18%) patients with AQP4-NMOSD died of the attack. For AQP4-NMOSD, Black race was overrepresented for attacks requiring ventilatory support vs those without these episodes (5 of 11 [45%] vs 88 of 457 [19%]; \(p = 0.045\)).
Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Mayo Clinic institutional review board. All patients or their parents consented to the use of their medical records for research purposes.

Autoantibody Testing

MOG-IgG and AQP4-IgG seropositivity for included patients was confirmed at the Mayo Clinic Neuroimmunology Laboratory (Rochester, MN) by live cell–based assay (MOG-IgG 8, AQP4-IgG 8), inactivated cell–based assay (AQP4-IgG 1), ELISA (AQP4-IgG 1), or tissue-based immunofluorescence (AQP4-IgG 1), as previously described. Both fresh and stored samples that were later retested were analyzed, and 5 of 8 (62.5%) patients with MOGAD and 2 of 11 (18%) with AQP4-NMOSD had the episodes before their respective antibody biomarkers were commercially available.

Identification of MOGAD and AQP4-NMOSD Attacks Needing Respiratory Support and Their Frequency

In this retrospective observational study, patients with MOGAD and AQP4-NMOSD seen at Mayo Clinic from January 1, 1996, to December 1, 2020, were identified through the Mayo Clinic neuroimmunology database. Their Mayo Clinic electronic medical records were then searched for terms relevant to attack-related requirement for respiratory support, and episodes occurring at Mayo Clinic or other medical facilities that were documented in our Mayo Clinic electronic medical record were included (Figure 1). The frequency of these episodes was defined as the number of patients with these attacks divided by the number of patients without these episodes in each group. Our inclusion criteria were (1) attack-related requirement for noninvasive (bilevel positive airway pressure or continuous positive airway pressure) or invasive respiratory support (mechanical ventilation); (2) MOG-IgG or AQP4-IgG positivity with fulfillment of MOGAD and AQP4-NMOSD clinical diagnostic criteria, respectively; and (3) sufficient clinical details. We excluded those with other reasons for respiratory support (Figure 1).

Data Collection

We abstracted sex and race from the electronic medical record, which is self-reported by patients at their initial visit to Mayo Clinic. Data on broad racial categories that could be selected by patients included the following: American Indian or Alaskan Native, Asian, Black or African-American (referred to as Black for this study), Native Hawaiian or Pacific Islander, other, or White. A separate ethnicity question included the designation as Hispanic or Latino or not Hispanic or Latino. Data on sex were self-selected as a binary of male or female sex (1996–2017), although since 2017 a third transgender category has also been available to select. Data on age at onset and comorbid conditions (respiratory, cardiovascular, hematologic and obesity) of included patients with MOGAD and AQP4-NMOSD with attacks requiring ventilatory support were abstracted from the demographics section and physician notes within the electronic medical record. We also stratified the timeline of episodes between those encountered from January 1, 1996, to December 31, 2009, and those that occurred from January 1, 2010, to December 1, 2020. In addition, we collected data on the indication for and duration of respiratory support, MRI findings, treatments, and outcomes. The racial category of those with attacks requiring respiratory support was compared to that of individuals without such attacks in MOGAD and AQP4-NMOSD. In those with attacks requiring respiratory support in MOGAD and AQP4-NMOSD, ventilatory support is rarely required.
support, we searched their medical records using the abbreviated term ‘financ’ to capture any financial hardship that could suggest socioeconomic contributors to a worse outcome and analyzed by race to explore whether any socioeconomic factors contributed to racial differences in outcome.

**Statistical Methodology**
Continuous and categorical variables were reported as median (range) and number (percent) and compared by use of the Wilcoxon rank-sum test and Fisher exact test, as appropriate (JMP Pro 14.1.0). Values of \( p < 0.05 \) were considered statistically significant.

**Data Availability**
Anonymized data used for this study are available on reasonable request from the corresponding author.

**Results**

**Patient Cohort, Timeline, and Frequency of Attacks Requiring Ventilatory Support**
A total of 19 patients were included (MOGAD 8, AQP4-NMOSD 11) who required ventilatory support from an attack at Mayo Clinic (\( n = 5 \)) or an outside facility (\( n = 14 \)). The majority of MOGAD episodes (7 of 8 [87.5%]) occurred from 2010 to 2020, while a minority of AQP4-IgG–NMOSD episodes (4 of 11 [36%]) occurred over this time period (\( p = 0.06 \)). Attack-related need for ventilatory support occurred in 8 of 279 (2.9%) patients with MOGAD vs 11 of 503 (2.1%) patients with AQP4-IgG–NMOSD (\( p = 0.63 \)). In those with race data available, Black race was overrepresented in patients requiring respiratory support with AQP4-NMOSD vs those who did not (5 of 11 [45%] vs 88 of 457 [19%]; \( p = 0.045 \)).
### Table 1 Demographics, Comorbid Conditions, and Attack Details From MOGAD and AQP4-NMOSD Attacks Requiring Respiratory Support

| Demographics                                                                 | MOGAD (n = 8)* | AQP4-NMOSD (n = 11)* | p Value |
|------------------------------------------------------------------------------|---------------|----------------------|---------|
| **Age at attack with RF, median (range), y**                                | 31.5 (5–47)   | 43 (14–65)           | 0.01    |
| **Pediatric (age <18 y at time of attack), n (%)**                          | 3/8 (38)      | 1/11 (9)             | 0.26    |
| **Female sex, n (%)**                                                        | 3/8 (38%)     | 10/11 (91%)          | 0.04    |
| **Racial category, n (%)**                                                   |               |                      |         |
| Whiteb                                                                       | 7/8 (88)      | 4/11 (36)            | 0.06    |
| Blackb                                                                       | 0/8 (0)       | 5/11 (45)            | 0.04    |
| **Comorbid conditions, n (%)**                                               |               |                      |         |
| Respiratory disease                                                          | 1/8 (13)c     | 2/11 (18)d           | 1       |
| Smoker                                                                       | 0/8 (0)       | 1/9 (11)             | 1       |
| Myasthenia gravis                                                            | 0/8 (0)       | 0/11 (0)             | NA      |
| Other                                                                        | 2/8 (25)e     | 6/11 (55)f           | 0.35    |
| **Attack and ventilatory details**                                           |               |                      |         |
| Episode represented first attack, n (%)                                      | 7/8 (88)      | 2/11 (18)            | 0.006   |
| Median EDSS score just before attack                                         | 0 (0–3.5)     | 4 (0–8)              | 0.02    |
| Encephalitis/rhombencephalitis, n (%)                                        | 8/8 (100)     | 2/11 (18)            | <0.001  |
| Quadriplegia, n (%)                                                           | 2/8 (25)      | 11/11 (100)          | 0.001   |
| Median time (range) from disease onset to episode, y                         | 0 (0–22)      | 3 (0–21)             | 0.02    |
| Median (range) duration of respiratory support, d                           | 2 (1–7)       | 19 (6–330)           | 0.01    |
| Mechanical ventilation, n (%)                                                | 8/8 (100)d    | 9/11 (82)h           | 0.49    |
| Noninvasive ventilation (BiPAP/CPAP), n (%)                                   | 0/8 (0)       | 2/11 (18)j           | 0.49    |
| Tracheostomy required, n (%)                                                 | 1/8 (13)l     | 5/11 (45)k           | 0.18    |
| Aspiration contributing to need for intubation, n (%)                        | 1/5 (20)      | 1/3 (33)             | 1.0     |
| Abnormal pulmonary imaging (CXR or CT of the chest), n (%)                   | 1/5 (20)m     | 2/3 (67)m            | 0.46    |
| ABG abnormal, n (%)                                                           | 1/3 (33)n     | 1/1 (100)           | 1.0     |
| Elevated hemi-diaphragm, n (%)                                               | 0/5 (0)       | 2/3 (67)             | 0.11    |
| Developed ventilator-associated pneumonia, n (%)                             | 1/5 (20)      | 1/3 (33)             | 1.0     |
| CSF analysis at the time of an attack, n (%)                                 |               |                      |         |
| Elevated white blood cell count (normal range, 0–5/μL)                       | 4/4 (100)p    | 3/3 (100)q           | NA      |

*Continued*
The risk of attack-related ventilatory support was not associated with other racial categories in the AQP4-NMOSD group or any racial category in the MOGAD group. Among the patients with MOGAD requiring ventilatory support, 1 of 4 with financial status documented reported financial hardship and was of White race and Hispanic ethnicity. Among the patients with AQP4-NMOSD requiring ventilatory support, 3 of 5 with financial status documented reported financial hardship, including 2 of Black race and 1 of Asian race.

### Clinical and Radiologic Characteristics of Attacks Requiring Respiratory Support

The demographics, clinical features, comorbid conditions, diagnostic tests, treatments, and outcome of patients with AQP4-NMOSD and MOGAD attacks requiring respiratory support are detailed in Table 2.

### Table 1: Demographics, Comorbid Conditions, and Attack Details From MOGAD and AQP4-NMOSD Attacks Requiring Respiratory Support (continued)

| Positive oligoclonal bands (≥2 unique CSF bands) | MOGAD (n = 8) | AQP4-NMOSD (n = 11) | p Value |
|------------------------------------------------|-------------|---------------------|--------|
| 0/3 (0)                                        | 0/2 (0)     | NA                  |        |

### Table 2: Treatments and Outcome From MOGAD and AQP4-NMOSD Attacks Requiring Respiratory Support

| Attack immunotherapy, n (%) | MOGAD (n = 8) | AQP4-NMOSD (n = 11) | p Value |
|------------------------------|---------------|---------------------|--------|
| IV corticosteroids           | 7/8 (88)      | 9/10 (90)           | 1      |
| PLEX                         | 2/8 (25)      | 9/10 (90)           | 0.01   |
| IVIG                         | 0/8 (0)       | 1/10 (10)           | 1.0    |

| Outcome                      | MOGAD (n = 8) | AQP4-NMOSD (n = 11) | p Value |
|------------------------------|---------------|---------------------|--------|
| Death, n (%)                 | 0/8 (0)       | 2/11 (18)           | 0.49   |
| Chronic tracheostomy (>6 mo) in those who survived, n (%) | 0/8 (0) | 1/9 (11) | 1 |
| Median (range) EDSS score in follow-up after attack | 1.25 (0–6.5) | 6.5 (3–10) | 0.002 |
| Recurrent attacks after ventilatory support episode in those surviving episode, n (%) | 6/8 (75) | 7/9 (78) | 1.0 |
| Median (range) time from ventilatory support episode to last clinical follow-up in those surviving episode, mo | 53 (3–121) | 42.5 (5–323) | 0.5 |

Abbreviations: ABG = arterial blood gas; AQP4-NMOSD = aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CXR = chest x-ray; EDSS = Expanded Disability Status Scale; IVIG = IV Immunoglobulin; MOGAD = Myelin Oligodendrocyte Glycoprotein antibody-associated disorder; NA = not applicable; PLEX = plasma exchange; RF = respiratory failure.

### Table 2: Treatments and Outcome From MOGAD and AQP4-NMOSD Attacks Requiring Respiratory Support

| Attack immunotherapy, n (%) | MOGAD (n = 8) | AQP4-NMOSD (n = 11) | p Value |
|------------------------------|---------------|---------------------|--------|
| IV corticosteroids           | 7/8 (88)      | 9/10 (90)           | 1      |
| PLEX                         | 2/8 (25)      | 9/10 (90)           | 0.01   |
| IVIG                         | 0/8 (0)       | 1/10 (10)           | 1.0    |

| Outcome                      | MOGAD (n = 8) | AQP4-NMOSD (n = 11) | p Value |
|------------------------------|---------------|---------------------|--------|
| Death, n (%)                 | 0/8 (0)       | 2/11 (18)           | 0.49   |
| Chronic tracheostomy (>6 mo) in those who survived, n (%) | 0/8 (0) | 1/9 (11) | 1 |
| Median (range) EDSS score in follow-up after attack | 1.25 (0–6.5) | 6.5 (3–10) | 0.002 |
| Recurrent attacks after ventilatory support episode in those surviving episode, n (%) | 6/8 (75) | 7/9 (78) | 1.0 |
| Median (range) time from ventilatory support episode to last clinical follow-up in those surviving episode, mo | 53 (3–121) | 42.5 (5–323) | 0.5 |

Abbreviations: AQP4-NMOSD = aquaporin-4 IgG seropositive neuromyelitis optica spectrum disorder; EDSS = Expanded Disability Status Scale; IVIG = IV Immunoglobulin; MOGAD = Myelin Oligodendrocyte Glycoprotein antibody-associated disorder; PLEX = plasma exchange.

*In those with details available.

**Optic neuritis n = 4, transverse myelitis n = 1, encephalitis with seizures n = 1.

Optic neuritis n = 2, transverse myelitis n = 4, unknown n = 1.
MOGAD and AQP4-NMOSD requiring respiratory support are summarized in Tables 1 and 2.

**Patients With MOGAD**

The attack requiring ventilatory support was the first attack in 7 (87.5%) and occurred as a subsequent relapse in 1 (12.5%) receiving fingolimod at that time for presumed multiple sclerosis (MS). The attack types and contributory clinical features leading to the need for airway protection included acute disseminated encephalomyelitis in 5 (status epilepticus 2, severe encephalomyelitis with quadriparesis 2, severe encephalitis 1) and unilateral cortical encephalitis in 3 (seizures/status epilepticus 3 [1 with temporary increased intracranial pressure of 600 mm H₂O requiring mannitol]). Concomitant acute bilateral optic neuritis occurred in 2. Antiseizure medications used included levetiracetam in 4, carbamazepine in 1, and valproic acid in 1. During attacks, MRI abnormalities included 1 or more of supratentorial T2 lesions (Figure 2, A.b and A.c) in 5, infratentorial T2 lesions in 4, spinal T2 lesions (all longitudinally extensive) in 3 (Figure 2, A.d), unilateral cortical swelling with T2 hyperintensity (Figure 2, A.a) and leptomeningeal enhancement in 3, and optic nerve enhancement in 2.

**Patients With AQP4-NMOSD**

The attack requiring ventilatory support was the first attack in 2 (18%) and occurred as a subsequent relapse in 9 (82%). In 7 of 9, details of maintenance treatments (if any) at the time of the attack were available: AQP4-NMOSD–targeted medications in 1 (mycophenolate mofetil and prednisone), MS-targeted medications in 3 (natalizumab and interferon beta 1), and no immunosuppressant medications in 3. The indications for ventilatory support included neurogenic respiratory failure or inability to protect airway from cervical myelitis and quadriparesis in 9 (82%), rhombencephalitis in 1 (9%), and a combination of both in 1 (9%). Concomitant attacks in other locations included area postrema syndrome (n = 2) and bilateral optic neuritis (n = 1). Notable acute MRI lesions included a longitudinally extensive spinal T2 lesion (Figure 2, B.c and B.d) in 7 of 7 available (median vertebral length 8, range 4–19; 6 of 7 [86%] extended to medulla [Figure 2, B.b, B.c, and B.d]) and infratentorial diffuse T2 lesion in 3 of 7 (43%; Figure 2, B.a).

**Discussion**

We found that MOGAD and AQP4-NMOSD attacks needing ventilatory support were rare. The indication for ventilatory support included neurogenic respiratory failure or inability to protect airway from cervical myelitis and quadriparesis with cervical myelitis, and invasive rather than noninvasive ventilation predominated in both groups. In AQP4-NMOSD, these episodes had higher morbidity and mortality, and those of Black race were more predisposed.

The frequency of respiratory failure in AQP4-NMOSD of 2.2% with a mortality of 18% that we report was less than in a 1999 NMO study in which 33% of patients with relapsing and 9% of patients with monophasic disease had respiratory failure with a mortality of 84%. The lower frequency we found may reflect the discovery of AQP4-IgG in 2004, allowing diagnosis of milder,
more limited forms of NMOSD and earlier use of more targeted attack-prevention immunosuppressants that may prevent these severe attacks. Frequent plasmapheresis use may account for our lower mortality, and early use with severe myelitis may prevent respiratory failure. It is notable that just 1 patient was receiving AQP4-NMOSD attack prevention treatment at the time of their attack, while 3 were taking MS treatments (natalizumab, interferon beta) known to worsen AQP4-NMOSD. The lack of availability of AQP4-IgG before 2004 and lower sensitivity of early-generation assays prevented many of these patients from being correctly diagnosed and treated and likely contributed to these events occurring. Disability before and after these severe attacks was greater in AQP4-NMOSD and may also increase respiratory failure from nonattack etiologies (e.g., aspiration pneumonia), but that was not the focus of this study. Patients with AQP4-NMOSD of Black race were predisposed to attack-related respiratory failure in our AQP4-NMOSD cohort, and this finding warrants emphasis. The frequency of attack-related requirement for ventilatory support may be higher in other AQP4-NMOSD cohorts with higher proportions of Black race. The increased risk of respiratory failure among Black patients in this study is consistent with many prior reports in AQP4-NMOSD that show that this racial group has a worse prognosis. For example, a prior study reported that those of African ancestry accounted for 41% of NMOSD cases but 90% of the mortality. We suspect that the worse outcome is most likely related to socioeconomic factors, including inequity in access to and quality of health care, which is partly supported by Black race predominating among those with respiratory failure who reported financial hardship. However, the small numbers limited full analysis of socioeconomic factors in this report, which is a major limitation of our study. A particular focus on ways to improve outcomes among Black patients with AQP4-NMOSD is needed given their predilection to both develop this disease and have a worse prognosis.

In MOGAD, these episodes were usually the first attack, which makes prevention difficult, but most did go on to have further relapses, suggesting that maintenance attack prevention immunosuppression in this subset of patients after a single severe life-threatening attack could be considered. Airway protection for seizures or severe encephalopathy predominated, including from the novel unilateral cortical encephalitis phenotype (Figure 2, A.a), highlighting that it is not always benign. These attacks occurred in 2.8% of patients with MOGAD with 0% mortality, while a prior study reported 3 of 48 (6.3%) with neurogenic respiratory failure (rhombencephalitis 2, myelitis 1) and 33% mortality, although encephalopathy or seizure indications were not reported. The better outcome in MOGAD vs AQP4-NMOSD may reflect the good recovery reported from most MOGAD attacks, better supportive treatment, and more MOGAD episodes occurring recently and most occurring as the first attack without preexisting disability. The lower proportion of MOGAD requiring plasma exchange may be from the more rapid recovery with shorter duration of intubation, better response to corticosteroids in MOGAD, and plasma exchange being better studied in AQP4-NMOSD. Study limitations include the retrospective design and potential for referral bias. In addition, in some patients, these diagnoses were assigned retrospectively on the basis of retesting of archived samples because these antibody biomarkers were not available for the entire study timeline (1996–2020), and it should be noted that AQP4-IgG was identified before MOG-IgG. This could have influenced both the total number of cases identified and their outcome. In the future, with earlier diagnosis and better disease-specific treatments, we expect that episodes may become less frequent and less severe. Attacks requiring ventilatory support occurring at outside facilities could have been underestimated if they were not documented in our electronic medical records. However, we did capture many episodes that occurred at other facilities, and such life-threatening attacks would be expected to be documented during a comprehensive neurology assessment at our facility. Finally, data on pulmonary aspects (e.g., chest imaging) were available in very few, limiting analysis of these aspects.

This study provides insight into a rare, life-threatening, attack-related complication of MOGAD and AQP4-NMOSD of which clinicians should be aware.

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conducted by VielaBio and Alexion. He is a consultant for Chugai, Roche, Genentech, and Mitsubishi Tanabe regarding clinical trials for NMO. S. Lopez-Chiriboga, D. Dubey, J.-M. Tillema, M. Toledano, and H. Yadav report no disclosures. E.P. Flanagan has served on advisory boards for Alexion, Genentech, and Horizon Therapeutics. He has received speaker honoraria from Pharmacy Times, royalties from UpToDate. He was a site primary investigator in a randomized clinical trial on Inebilizumab in neuromyelitis optica spectrum disorder run by Medimmune/Viela-Bio/ Horizon Therapeutics. He has received funding from the NIH (R01NS113828), is a member of the medical advisory board of the MOG project and an editorial board member of the Journal of the Neurological Sciences and Neuroimmunology Reports. Go to Neurology.org/N for full disclosures.

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Appendix Authors

| Name                  | Location               | Contribution                                                                 |
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| Cristina Valencia Sanchez, MD, PhD | Mayo Clinic, Rochester, MN | Analyzed and interpreted the data; revised the manuscript for intellectual content. |
| Elia Sechi, MD | Mayo Clinic, Rochester, MN | Statistical analysis; interpreted the data; revised the manuscript for intellectual content. |
| Jery Inbarasu, MD | Mayo Clinic, Rochester, MN | Designed and conceptualized study; drafted the manuscript; analyzed and interpreted the data. |
| Eelo F. Wijdicks, MD, PhD | Mayo Clinic, Rochester, MN | Interpreted the data; revised the manuscript for intellectual content. |
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Appendix (continued)

| Name                  | Location               | Contribution                                                                 |
|-----------------------|------------------------|------------------------------------------------------------------------------|
| Jan-Mendelt Tillema, MD | Mayo Clinic, Rochester, MN | Interpreted the data; revised the manuscript for intellectual content. |
| Michel Toledano, MD | Mayo Clinic, Rochester, MN | Interpreted the data; revised the manuscript for intellectual content. |
| Hemang Yadav, MD | Mayo Clinic, Rochester, MN | Interpreted the data; revised the manuscript for intellectual content. |
| Eoin P. Flanagan, MD | Mayo Clinic, Rochester, MN | Designed and conceptualized study; analyzed and interpreted the data; revised the manuscript for intellectual content; study supervision. |

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