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Short Communication

# Autoimmune encephalitis and delayed diagnosis in common variable immunodeficiency: A case report and review of literature

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ABSTRACT

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency disorder that often presents with recurrent infections and autoimmune complications, leading to diagnostic delays. This case report presents two adult male patients, ages 44 and 42, with prolonged histories of recurrent pneumonia, sinusitis, meningitis, and autoimmune encephalitis. Both cases were initially mismanaged due to the isolated treatment of symptoms, delaying the diagnosis of CVID. Comprehensive diagnostic evaluations eventually revealed low immunoglobulin levels, confirming the diagnosis. These cases highlight the importance of early recognition and a multidisciplinary approach to managing patients with recurrent infections and unusual presentations.

## 1. Introduction

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by repeated infections, autoimmune disorders, and gastrointestinal complications but usually with considerable diagnostic delay and mismanagement (Ameratunga et al., 2021). In part, this heterogeneity of the features in CVID is because of the fact that symptoms may often mimic those of other disorders, making early diagnosis quite a challenge (Yazilik et al., 2014). For example, recurrent sinopulmonary infections, which include sinusitis and pneumonia, are the more frequent presentations among T-cell lymphopenic patients; these are usually treated separately from one another (Esmaeilzadeh et al., 2023). The other complications of the clinical diagnosis include autoimmune disorders and gastrointestinal problems, leading to a difficult diagnosis without an overall comprehensive and integrated diagnostic approach (Agarwal and Cunningham-Rundles, 2019). We report two cases in whom the isolated treatment of clinical episodes delayed the diagnosis of CVID, with severe complications, thus stressing the need for increased clinical awareness and a multidisciplinary approach for patients with recurrent infections and atypical clinical presentations (Uzzan et al., 2016).

## 2. First case presentation

A 44-year-old man was referred for a splenectomy consultation and evaluation with a history of chronic productive cough and intermittent fever. Physical examination of the patient revealed erythematous lesions and erosions in the oral cavity; the throat and the tonsils were erythematous. The left side of the thorax showed a surgical scar from the previous lobectomy. Rales were auscultated in the left lung. He had a nasal speech, which was reasoned to be due to congestion from recurrent sinusitis. The abdomen was soft, with a palpable spleen but no hepatomegaly. The rest of the examination was unremarkable. His medical history was significant for chronic enteritis-like diarrhea that had been ongoing for more than two decades, during which time several evaluations ruled out liver cirrhosis and celiac disease. The history included recurrent pneumonia: one episode ten years ago, with severe pneumonia, empyema, and bronchiectasis, managed with lobectomy and mediastinal lymphadenectomy. Other medical history includes limbic encephalitis, treated as herpetic encephalitis involving the temporal lobe the previous year; symptoms include fever, progressive headache, proximal muscle pain, nausea, vomiting, altered mental status characterized by bizarre behaviors, impaired consciousness, disorientation, dysphasia, and delusions. Herpetic encephalitis was not documented;

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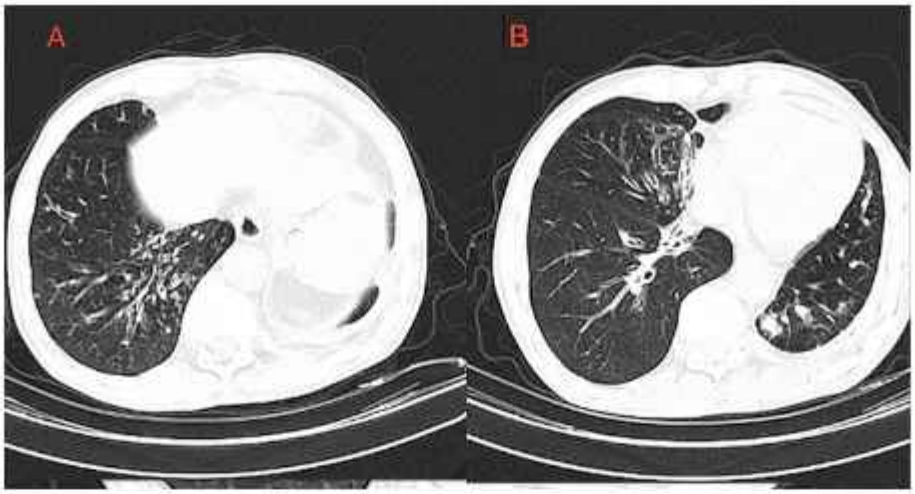


**Fig. 1.** A: Right lower lobe bronchiectasis B: Right middle lobe bronchiectasis and scattered centrilobular nodules in left lung.

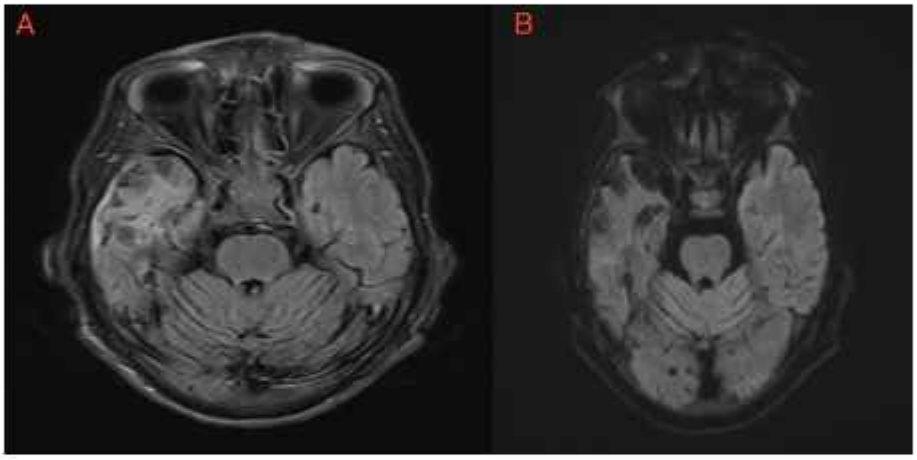


**Fig. 2.** Heterogeneous high signal intensity in right temporal lobe in fluid attenuated inversion recovery (A) without restriction in diffusion-weighted MRI (B) showing remote necrotizing encephalitis.

however, the MRI of the brain did reveal necrotizing encephalitis of the temporal lobe. He stated that he had experienced similar symptoms seven years earlier. The patient gave a history of smoking 30 pack-years with no history of alcohol or substance use. His medications included quetiapine, montelukast, tiotropium, valproate sodium, and lorazepam. Extensive work-ups were carried out before admission, in view of the history of a bone marrow biopsy showing a normocellular marrow with a polymorphic population of hematopoietic cells. The patient has been experiencing recurrent respiratory infections since he was an adolescent, and he also has bronchiectasis [Fig. 1], chronic diarrhea, and encephalitis [Fig. 2]; therefore, a wide differential diagnosis including inborn errors of immunity and primary immunodeficiency disorders was considered. In this case, in the presence of considerably low levels of immunoglobulin [IgG: 200 mg/dL], CVID was diagnosed. All the primary and secondary causes thereafter were considered for investigation in detail [Table 1]. Anti-tetanus antibody level was low in the patient, and following a single-dose administration of the Td vaccine, the serum anti-tetanus antibody titer did not reach an optimal value even after two weeks. These findings confirm the diagnosis of CVID after exclusion of all secondary etiologies.

## 3. Second case presentation

A 42-year-old male was referred for further investigation following brain biopsy. The patient had been admitted two months earlier following a generalized seizure, which was preceded by a one-week prodrome of malaise, frontal headache, behavior change, and unsteadiness with loss of consciousness and seizure. A probable diagnosis of brain tumor after five days hospitalization with further evaluations in other centers ended up with hippocampectomy. During the surgery, biopsy was obtained from the temporal lobe brain mass, with suspicion of ganglioglioma. In his examination, GCS was 15; temperature was 38.7 °C; heart rate was 100 bpm. There is no nuchal rigidity, and no focal neurological deficits were recorded. Examination of lungs, heart, abdomen, and other organs, nothing was to be remarked upon. He mentioned in his story that he had acute meningitis 12 years ago, presenting with fever, headache, cough, photophobia, and vomiting. The CSF study then showed WBC: 8000 cells/μL, PMN dominant, glucose: 15 mg/dL, protein: 224 mg/dL. He was given a treatment of 14 days with antimicrobials. Electrolyte levels, glucose, and CBC were within normal limits [Table 2]. Another episode of meningitis was stated in early childhood, which was treated without complication. His past history was also notable, with frequent undocumented hospitalizations since 7 years of age due to sinus and lung infections. He smoked 3–4 cigarettes a day for the last three years and once a week used hookah. Azithromycin or levofloxacin was used periodically, during sinusitis or lung infections, and he did not report the use of other medications. The patient was investigated for autoimmune encephalitis, wherein partial pleocytosis

**Table 1**
: Paraclinical test results for patient one with AB-positive blood type and BMI = 19.

| Test Category | Parameter | Before Hospitalization | During Hospitalization | Reference Range |
|---|---|---|---|---|
| Complete Blood Count | | | | |
| | White Blood Cells | 8.1 × $10^3$/L | 6.8 × $10^3$/L | 4–10 × $10^3$/L |
| | Polymorphs (%) | 92 % | 56 % | – |
| | Lymphocytes (%) | 6 % | 33 % | – |
| | Monocytes (%) | 2 % | 6 % | – |
| | Red Blood Cells | 4.91 × $10^6$/μL | 4.45 × $10^6$/μL | – |
| | Hemoglobin | 11.5 g/dL | 10.6 g/dL | 14–18 g/dL |
| | Hematocrit | 37.5 % | 34.7 % | 39–52 % |
| | Mean Corpuscular Volume | 76 fL | 77.98 fL | 80–96 fL |
| | Mean Corpuscular Hemoglobin | 23 pg | 23.82 pg | 26–32 pg |
| | MCH Concentration | 31 g/dL | 30.55 g/dL | 32–36 g/dL |
| | RDW | 14.49 % | 14.1 % | 11–16 % |
| | Platelets | 202,000 /μL | 218,000 /μL | 150,000–450,000 /μL |
| Lumbar Puncture | | | | |
| | Appearance | Clear | Clear | – |
| | Color | Colorless | Colorless | – |
| | WBC | 130 /μL | 4 /μL | – |
| | RBC | 30 /μL | – | – |
| | LDH | 20 IU/L | 66 IU/L | – |
| | Wright | Negative | Negative | – |
| | Sugar | 52 mg/dL | 55 mg/dL | – |
| | Protein | 87 mg/dL | 29 mg/dL | – |
| Serology | | | | |
| | TSH | 3.7 μIU/mL | – | 0.32–6 μIU/mL |
| | Creatinine | 0.6 mg/dL | 0.8 mg/dL | 0.9–1.4 mg/dL |
| | LDH | 475 IU/L | 353 IU/L | <480 IU/L |
| | NBT | – | 80 % | >90 % |
| | Autoimmune Encephalitis Panel[a] | – | All Negative | – |
| | Anti-TPO | 23 IU/mL (Negative) | – | <40 IU/mL (Negative) |
| | IgG | – | 200 mg/dL | – |
| | IgA | 95 mg/dL | – | 83–406 mg/dL |
| | Galactomannan | 0.35 ng/mL (Negative) | – | <0.5 Negative |
| | Aspergillus IgG | – | 0.7 NTU | <9 Negative |
| | Aspergillus IgM | – | 0.1 NTU | <9 Negative |
| | Tetanus Antibody | – | 0.4 IU/mL | 0.1–0.5 IU/mL |
| | Diphtheria Ab (IgG) | – | Negative | – |
| | Anti-DNA | – | 19.7 | <39 Negative |
| | SSA/Ro IgG | – | <1 AU/mL | <16 Negative |
| | SSB/La IgG | – | <1 AU/mL | <16 Negative |
| | ANA | – | Negative (<1:40) | – |
| | Rheumatoid Factor | – | 2.7 AU/mL | <20 AU/mL |
| | Anti-tTG | 1.2 AU/mL | – | <12 Negative |
| | HSV IgM | Negative | – | – |
| | HIV ELISA | Negative | – | – |
| | JAK2-V617F | Negative | – | – |
| Flow Cytometry | CD markers (% positive) | CD3:15 %, CD4:8 %, CD8:7 %, CD10:NEG, CD19:5 %, CD20:5 %, CD22:4 %,cd117:1 %, CD33:42 %, CD11b:60 %, CD14:9 %, CD64:40 %, CD34:1 %, HLA-DR:12 % | – | – |
| Imaging | Abdominal Ultrasound | Portal vein: 15 mm, Spleen span: 195 mm | – | – |
| Pathology | Bone Marrow Biopsy | Normocellular marrow with polymorphic hematopoiesis cells | – | – |

[a] GABARB1/B2,AMPA1/2,LGI1,CASPR2,Anti-Glutamate Receptor IgG(Type NMDA).

was observed in tests. CT cisternography showed the presence of pansinusitis (Fig. 3). Isohemagglutinin and complement levels were measured and isohemagglutinin B was found to be negative although the blood type of the patient was A+ that must have arisen from IgG production. Complement levels were within normal limits (Table 3): C3, C4, and CH50. No properdin deficiency was noted; properdin deficiency is a condition related to the risk of developing severe meningococcal infection. Levels of IgG, IgA, and IgE were low (Table 3). The anti tetanus antibody level was found to be low; after one dose of the Td vaccine, his antibody titers were suboptimal after one month. The diagnosis of CVID was a suggestion based on history of sinusitis, the recurrent meningitis, low immunoglobulin levels, and a prolonged course of illness.

## 4. Discussion

In the first misdiagnosed case, the patient had a history of chronic diarrhea for a period of 20 years, recurrent pneumonia (including one episode necessitating a lobectomy), two decades of sinusitis, and two episodes of autoimmune encephalitis that were initially treated as herpetic encephalitis (Esmaeilzadeh et al., 2023). The primary diagnostic challenge was the occurrence of recurrent infections with overlapping symptoms. Without a comprehensive and integrated diagnostic approach, each episode was managed in isolation, likely contributed to the delayed recognition of the underlying immunodeficiency disorder (Ameratunga et al., 2021). In the second misdiagnosed case, the patient

**Table 2**
Paraclinical test results for second patient During hospitalization in ICU with A-positive blood type and BMI = 18.

| Parameter | Value | Unit | Reference Range |
|---|---|---|---|
| WBC | 7200 | cells/μL | 4000-11,000 |
| Seg | 63.6 % | % | 40–70 % |
| Lym | 27.9 % | % | 20–45 % |
| Mixed | 8.5 % | % | 2–10 % |
| HG | 13.7 | g/dL | 12.0–16.0 |
| MCV | 81.7 | fL | 80–100 |
| MCH | 24.6 | pg | 27–33 |
| MCHC | 30.1 | g/dL | 32–36 |
| PLT | 266,000 | platelets/μL | 150,000-450,000 |
| INR | 1.0 | ratio | 0.9–1.2 |
| PT | 12 | sec | 11–13.5 |
| PTT | 28 | sec | 25–35 |
| FBS | 70 | mg/dL | 70–100 |
| BUN | 8.6 | mg/dL | 7–20 |
| CR | 0.9 | mg/dL | 0.5–1.2 |
| NA | 143 | mEq/L | 135–145 |
| K | 4.2 | mEq/L | 3.5–5.0 |
| HIV AB | Negative | – | – |

had a 35-year history of frequent sinus and pulmonary infections and meningitis and recurrent hospitalizations since childhood (Sanchez et al., 2023). Management of each clinical episode in isolation contributed to delay in diagnosis of CVID (Yesillik et al., 2014). IgG deficiency most often manifests as recurrent sinopulmonary infections in the form of sinusitis, otitis media, bronchitis, and pneumonia among CVID patients (Esmaeilzadeh et al., 2023). The most common features reported to date are that 90 % have one episode of acute lower respiratory tract infection in their lifetime, 89 % have chronic sinusitis, and 70 % develop recurrent otitis media (Agarwal and Cunningham-Rundles, 2019). Therefore, recurrent sinopulmonary infections in a patient should raise suspicion of an underlying immunodeficiency (Ameratunga et al., 2021). Diarrhea is the most common gastrointestinal symptom in CVID patients. Although the gastrointestinal manifestations of CVID are heterogeneous and can mimic other well-known diseases such as celiac disease, pernicious anemia, and inflammatory bowel disease, there are significant histopathological differences [5]. Non-infectious enteropathy in patients with CVID occurs in about 10–12 % of them [7]. Additionally, these immunodeficient patients are also more prone to acute or chronic *Giardia lamblia* infections, which is one of the most common pathogens that cause diarrhea in CVID patients [6]. Chronic norovirus and Campylobacter infections are also frequently observed in these patients [5]. One of the most interesting features in the first patient was the development of two episodes of limbic encephalitis, which were initially treated as herpetic encephalitis. Although limbic encephalitis is not exclusively caused by herpesviridae reactivation, these viruses remain among the most severe and treatable causes of acute encephalitis (Jacob et al., 2021). In view of the fact that encephalitis has recurred and subsequent CVID, autoimmune encephalitis or antibody-mediated encephalitis becomes a more probable etiology (Agarwal and Cunningham-Rundles, 2019). About 20 % of CVID patients develop one or more autoimmune disorders, probably because of the concomitant occurrence of both abnormal immune regulation and immunodeficiency (Fevang, 2023). Autoimmune encephalitis (AIE) represents a heterogeneous group of neurological disorders characterized by cognitive and behavioral impairments due to the immune response against neuronal antigens (Jacob et al., 2021). Although AIE accounts for 21 % of all encephalitis cases, its occurrence in CVID patients is rarely documented. In particular, it is quite under documented as an autoimmune encephalitis presenting as a single clinical manifestation of CVID (Azizi et al., 2018). Therefore, a comprehensive diagnostic perspective is crucial when evaluating patients, especially those with recurrent sinopulmonary infections or other atypical presentations such as encephalitis (Ameratunga et al., 2021). These cases may have underlying autoimmune etiologies beyond common infectious causes, necessitating consideration of primary immune deficiencies or genetic disorders (Gupta et al., 2019). Immunoglobulin replacement therapy, intravenous, or subcutaneous forms the cornerstone in the management of CVID. Both techniques are similarly effective and safe in the context of

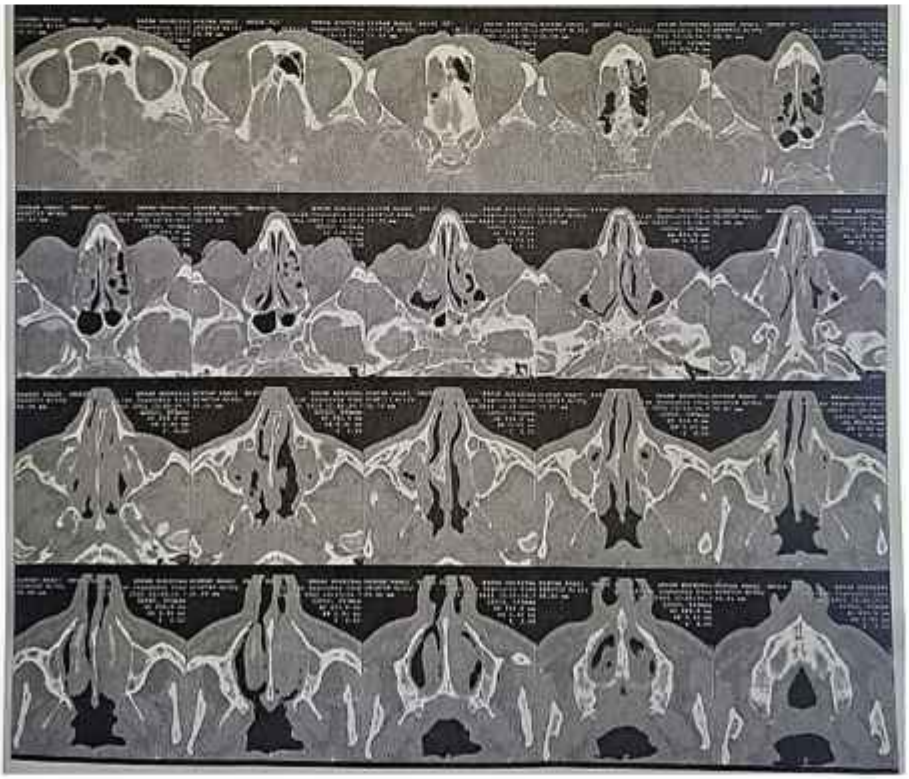

**Fig. 3.** Pansinusitis was observed in cisternography.

**Table 3**
Paraclinical test results the second patient After discharge from the hospital (complement, Immunoglobulin, Isohemoglobin, Autoimmune encephalitis panel).

| Test/Panel | Result | Unit | Reference Range |
|---|---|---|---|
| Complement | | | |
| C3 | 135 | mg/dL | 75–187 |
| C4 | 26 | mg/dL | 9–38 |
| CH50 | 110 | % | 51–151 |
| Immunoglobulins | | | |
| IgG | 218 | mg/dL | 700–1600 |
| IgA | 19 | mg/dL | 71–360 |
| IgE | 3.4 | mg/dL | Adult <160 |
| Serology | | | |
| Isohemoglobin | Negative | – | Compare with blood group |
| GABARB1/B2 (IFA Titer) | Negative | – | <1/10 Negative |
| AMPA1/2 (IFA Titer) | Negative | – | <1/10 Negative |
| DPPX (IFA Titer) | Negative | – | <1/10 Negative |
| LGII (IFA Titer) | Negative | – | <1/10 Negative |
| CASPR2 (IFA Titer) | Negative | – | <1/10 Negative |
| ANTI-GLUTAMATE RECEPTOR IgG | Negative | – | <1/10 Negative |
| Vaccination | | | |
| Tetanus ab (IgG) | 0.31 | IU/mL | >5 IU/mL |
| Tetanus ab (Post-vaccination) | 0.1 | IU/mL | – |
| Flow Cytometry | | | |
| CD10 | 0.6 | % | – |
| CD19 | 6.3 | % | – |
| CD20 | 8.0 | % | – |
| CD4/8 Ratio | 1.3 | ratio | – |
| CD3 | 64.0 | % | – |
| CD16 + 56 | 10.9 | % | – |
| CD3−/16 + /56 + | 11.5 | % | – |
| CD56 | 12.7 | % | – |

replacement therapy. Monitoring of serum IgG levels should be performed every six months, with dose adjustments according to the patient's weight and IgG production. In cases with bronchiectasis and/or COPD, antibiotic prophylaxis is necessary in order to decrease respiratory exacerbations, but also the addition of antibiotics during acute infective episodes. Such specific therapy includes, among others, the use of azithromycin, 250 mg three times a week, to reduce the frequency of exacerbations of sinopulmonary infections. Generally, vaccination is safe in immunodeficient patients but may be less effective in severely antibody-deficient patients or combined immunodeficiency patients who are undergoing immunosuppressive therapy or immunoglobulin replacement. Of these, live vaccines pose the highest risk among the severely immunocompromised; therefore, their use must be carefully considered.

(Fevang, 2023).

## 5. Conclusion

Case 1 had recurrent, varied, and chronic GI, sinopulmonary, and CNS symptoms, associated with splenomegaly, and he was diagnosed to have CVID at the age of 44 years. Case 2 presented with recurrent sinopulmonary and brain infections; he had a history of insidious hospitalization since the age of 7 years and his disease was managed piecemeal episodically without realizing the cause for his repeated infections. In such a case, what is important is the tendency to consider each episode as separate and, with that, probably bypassing the wide spectrum of disorders that could explain such manifestations taken together.

## CRediT authorship contribution statement

**Mastoorch Sagharichi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Amin Aalipour:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elahe Eghbal:** Writing – review & editing. **Farid Javandoust Gharehbagh:** Writing – review & editing. **Roozbe Shadidi Asil:** Conceptualization. **Ilad Alavi Darazam:** Conceptualization.

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## Declaration of competing interest

None declared.

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## Data availability

Data will be made available on request.

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