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## Human Metapneumovirus Infection in Adults as the Differential Diagnosis of COVID-19

### COVID-19 Ayırıcı Tanısı Olarak Yetişkinlerde İnsan Metapnömovirüs Enfeksiyonu

**ABSTRACT** Human metapneumovirus (HMPV) is a respiratory tract virus identified 18 years prior to SARS-CoV-2. Both viruses cause acute respiratory failure characterised by a rapid onset of widespread inflammation in the lungs with clinical symptoms similar to those reported for other viral respiratory lung infections. HMPV, more generally known as childhood viral infection, causes mild and self-limiting infections in the majority of adults, but clinical courses can be complicated in risky groups and associated morbidity and mortality are considerable. Moreover, adults are not regularly screened for HMPV and the prevalence of adult HMPV infections in Turkey is unknown, with previous reports in the paediatric population. This should always be kept in mind during the COVID-19 pandemic, particularly when neurological complications are added to respiratory findings. In our study, two adult cases of HMPV pneumonia and encephalitis have been recorded.

**Keywords:** Acute respiratory infections, neurological involvement, wide respiratory screening

**ÖZ** İnsan metapnömovirüs (HMPV), SARS-CoV-2'den 18 yıl önce tanımlanan yeni solunum yolu virüsüdür. Bilinen diğer viral solunum yolu enfeksiyonlarına benzer klinik semptomlarla sahip olup, her iki virüs de akut solunum yetmezliğine neden olabilir. HMPV çocukluk çağı solunum yolu enfeksiyonu olarak bilinsede, yetişkinlerin çoğunda hafif ve kendini sınırlayan enfeksiyonlara neden olur, hatta riskli hastalarda klinik seyir komplike olup ciddi morbidite ve mortaliteye neden olabilir. Yetişkinler viral enfeksiyon durumunda rutin olarak HMPV için taranmadığından Türkiye'de HMPV enfeksiyonlarının prevalansı bilinmemektedir ve önceki rapor edilen olgular pediatrik popülasyonda yer almaktadır. COVID-19 pandemisi sırasında özellikle solunum bulgularına nörolojik komplikasyonlar eklendiğinde akıld tutulmalıdır. Bu raporda HMPV pnömonisi ve ensefaliti olan iki yetişkin olguyu sunmaktayız.

**Anahtar Kelimeler:** Akut solunum yolu enfeksiyonları, Nörolojik tutulum, Geniş respiratuvar tarama

## Introduction

Human metapneumovirus (HMPV) is a respiratory tract virus identified 18 years before SARS-CoV-2. Both viruses cause acute respiratory failure characterized by rapid onset of widespread inflammation in the lungs with clinical symptoms similar to those reported for other viral respiratory lung infections. (1) HMPV is known as childhood infection, but can cause life-threatening infections especially in the frail elderly and the immunocompromised patients. (2, 3) Adults are not routinely screened for HMPV and prevalence of adult HMPV infections in Turkey is unknown, previous reports were in the pediatric population. However, it should always be kept in mind during COVID-19 pandemic especially when neurological complications are added to respiratory findings. We report two adult cases with HMPV pneumonia and encephalitis.

## Cases

A first case was a 69-year-old woman with hypertension and Addison's disease. She was admitted to a hospital with fever and dyspnea during SARS-CoV-2 pandemic. At hospital admission, her level of consciousness and the neurological examination was normal. She was transferred directly to our ICU due to respiratory failure and non-invasive mechanical ventilation (NIMV) support with a helmet mask was started. Reverse real-time transcriptase polymerase chain reaction (PCR) for COVID-19 was negative and chest computed tomography (CT) was compatible with viral pneumonia. (Figure 1) During COVID-19 outbreak because of the situations where the first PCR for COVID-19 can be negative, we initially started treatment against SARS-CoV-2. However, as the respiratory failure progressed she was intubated on the 3th ICU day. Antibiotherapy was changed to piperacillin/tazobactam + vancomycin. Mechanical ventilation was started with PCV mode, PC 16cmH<sub>2</sub>O, PEEP 10cmH<sub>2</sub>O, FiO<sub>2</sub> 70%, but respiratory acidosis and hypoxia persisted and prone ventilation has been used. She was prescribed 5 mg prednisolone due to Addison's disease, steroid treatment of stress dose was arranged by consulting endocrinology. Laboratory tests showed lymphopenia and elevated inflammatory markers. A nasopharyngeal swab specimen was identified as positive for HMPV using duplex reverse transcription PCR. On the 11.th day the inflammatory markers were almost normalized and chest X-ray was better, so sedoanalgesia was gradually reduced.

However, 48h following cessation of all sedation the patient did not regain consciousness and neurology consultation was performed. Cranial magnetic resonance imaging (MRI), including diffusion-weighted and contrast-enhanced series showed bilateral frontal signal changes compatible with meningoencephalitis. MRI findings were suggestive of acute encephalitis with a concomitant acute demyelinating process. Lumbar puncture revealed normal glucose and high protein levels, cell count, IgG index and albumin were within normal limits and no viruses could be isolated in the cerebrospinal fluid (CSF). Oligoclonal bands were negative. Intravenous corticosteroid treatment (1mg/kg/24h) followed by plasmapheresis with albumin was initiated and performed on alternate days for five cycles. The patient developed generalized tonic-clonic seizure, so sedation was deepened with thiopental, midazolam and fentanyl. General condition of the patient worsened, lymphopenia and inflammatory marker elevation persisted with refractory fever around 40C. All potential infectious sources were ruled out, antibiotherapy was escalated and inotropic support has been increased significantly. However, cardiac arrest developed on the 16th ICU day, and CPR was unsuccessful.

The second case was an 82-year-old woman with atrial fibrillation and hypertension. She presented fever and worsening dyspnea, a diagnosis of viral pneumonia was confirmed by chest CT. Reverse real-time transcriptase PCR for SARS-CoV-2 was negative. She was hospitalized directly in the ICU and started NIMV support with a helmet mask. During coronavirus pandemic we started treatment accepting patients as PCR positive for COVID-19 without waiting for the result. Laboratory tests showed lymphopenia and elevated inflammatory markers. On the third day of admission, her respiratory failure required endotracheal intubation and mechanical ventilation (PC mode, PC 20cmH<sub>2</sub>O, PEEP 14cmH<sub>2</sub>O, FiO<sub>2</sub> 50%). A nasopharyngeal swab specimen was identified as negative for COVID-19 and positive for HMPV. On the 12th of ICU day with the normalization of infectious markers and improvement of chest X-ray, sedation was gradually reduced and stopped. She was awake with delirium which couldn't be explained by any metabolic occurrence, and was extubated under maximum doses of haloperidol and dexmedetomidine. Neurology consultation was performed, but MRI or LP wasn't performed due to the lessening of symptoms. The patient was discharged to a ward on the 14th day of ICU treatment. Agitation decreased but persisted despite treatment even after discharged to

a ward. The patients remained physically and cognitively impaired despite rehabilitation. The neuropsychological assessment showed mild difficulties on social abilities.

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## Discussion

To the best of our knowledge, this is the first case report of human metapneumovirus infection in adults from Turkey. Our first case support consideration of HMPV as a causative agent of acute central nervous system involvement after respiratory tract infection in adults. The clinical presentation, laboratory and CSF results, and radiologic findings supported the diagnosis of encephalitis. CSF examinations showed elevated protein with no marked pleocytosis typically seen in viral encephalitis and similar to cases of COVID-19-related CNS involvement. (4) The presence of severe agitation in the second case suggests CNS involvement, but we do not have MR and LP evidence to support this hypothesis.

HMPV infection can not be distinguished from other respiratory viruses on clinical and laboratory findings only (5). Compared to other respiratory viruses it has similar rates of ICU admission, mechanical ventilation, and length of stay for hospitalization (6). Neurotropic potential of HMPV seems to be one of the main pathologic mechanisms of these infections. Central nervous system involvement is documented in both children and adults (7, 8, 9). Moreover, in many cases of encephalitis of unknown etiology, HMPV has been simultaneously detected in the respiratory tract.

The mechanism by which the CNS is affected by the virus is unclear, and treatment approaches are not well defined (10). The fact that we could not demonstrate the virus from CSF may point toward the role of autoimmune inflammatory response as the pathogenic factor in central nervous system involvement or the timing of viral isolation from CSF had passed.

HMPV at present is still without specific antiviral therapy and managing HMPV-encephalitis is a challenge for intensivists (11). Current clinical management as with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen or mechanical ventilatory support, and advanced supportive therapy like plasmapheresis and steroid therapy when indicated.

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## Conclusion

The presented cases emphasize the importance of a wider respiratory screening in viral pneumonias. HMPV should be kept in mind when no other etiological agent can be found in the presence of viral pneumonia and central nervous system involvement findings. Determination of the etiological agent may prevent the use of unnecessary antibiotics. Further studies and treatment strategies are necessary to augment the therapeutic approach in these patients.

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