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CASE REPORT

Middle East respiratory syndrome coronavirus in pediatrics: a report of seven cases from Saudi Arabia

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Abstract **Infection with Middle East respiratory syndrome coronavirus (MERS-CoV) emerged in 2012 as an important respiratory disease with high fatality rates of 40%–60%. Despite the increased number of cases over subsequent years, the number of pediatric cases remained low. A review of studies conducted from June 2012 to April 19, 2016 reported 31 pediatric MERS-CoV cases. In this paper, we present the clinical and laboratory features of seven patients with pediatric MERS. Five patients had no underlying medical illnesses, and three patients were asymptomatic. Of the seven cases, four (57%) patients sought medical advice within 1–7 days from the onset of symptoms. The three other patients (43%) were asymptomatic and were in contact with patients with confirmed diagnosis of MERS-CoV. The most common presenting symptoms were fever (57%), cough (14%), shortness of breath (14%), vomiting (28%), and diarrhea (28%). Two (28.6%) patients had platelet counts of < 150 × 10^9/L, and one patient had an underlying end-stage renal disease. The remaining patients presented with normal blood count, liver function, and urea and creatinine levels. The documented MERS-CoV Ct values were 32–38 for four of the seven cases. Two patients (28.6%) had abnormal chest radiographic findings of bilateral infiltration. One patient (14.3%) required ventilator support, and two patients (28.6%) required oxygen supplementation. All the seven patients were discharged without complications.**

Keywords Middle East respiratory syndrome coronavirus; MERS-CoV; pregnancy; pediatrics

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was initially described and detected in 2012 in a patient from the Kingdom of Saudi Arabia (KSA) [1]. Infection with this virus exhibits high fatality rates of 40%–60% [2–5]. The number of cases affected with MERS-CoV reached 2015, and 703 patients died of the resulting disease [6]. The hallmark of the disease is the predominance of transmission in health-care settings [2,3,7–13], where human-to-human transmission is the main route of transmission and causes the majority of cases. In community settings, the transmission of MERS-CoV has been believed to occur from dromedary camels to humans. Community transmissions also occur in household settings [14]. Another feature of the disease is the occurrence of few cases among children [4,15]. The first reported case in the pediatric age group involved a child from Jeddah, KSA on June 28, 2013 [16]. A recent review included 31 pediatric MERS-CoV cases within a 5-year period [17]. In a study on 2235 children with acute viral respiratory infections, none was tested positive for MERS-CoV [18]. From 2012 to 2015 in KSA, a total of 1250 patients were reported to have MERS-CoV infection, and 3.3% of them aged less than 10 years [19]. In another analysis of 109 cases between April 23, 2014 and August 31, 2015, 4.2% of the patients aged less than 20 years [20]. From April 2015 to February 2016, 57 363 residents (18.4/10 000) were suspected with and tested positive for MERS-CoV infection in KSA, and only 0.7% was tested

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positive for MERS-CoV infection [21]. In the same period, 10 (0.1%) of 8032 children aged less than 14 years were positive for MERS-CoV [21]. In 2015, the case definition included a specific description of children who needed testing and those who were exposed to camels or camel products or to a confirmed or suspected MERS case and children with unexplained severe pneumonia [22]. In this paper, we present the clinical and laboratory features of seven pediatric patients.

Presentation of cases

We collected the clinical and laboratory data of pediatric patients admitted to Prince Mohamed Bin Abdulaziz Hospital (PMAH), Ministry of Health, Riyadh, KSA. Nasopharyngeal swabs (NPSs) were tested for MERS-CoV by using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) as described previously [4,23,24]. The PCR test amplifies the upstream E protein (upE gene) and ORF1a of MERS-CoV. A positive test was considered when both assays were positive, and the samples were considered negative when the MERS-CoV RT-PCR was negative [4].

From April 2014 to November 2016, 295 patients of definite MERS were admitted to PMAH. Of these patients, seven (2.4%) were children ($<$ 18 years) (Table 1), and 57% were female aged between 8 months and 16 years. One patient had bronchial asthma and chronic renal disease, and another patient had sickle cell disease. The five other cases had no underlying illnesses.

Of the seven cases, four patients sought medical advice within 1–7 days from the onset of symptoms. The other three (43%) patients were asymptomatic and were in contact with confirmed patients who acquired MERS-CoV.

The most common presenting symptoms were fever (57%), cough (14%), shortness of breath (14%), diarrhea (28%), and vomiting (28%) (Fig. 1).

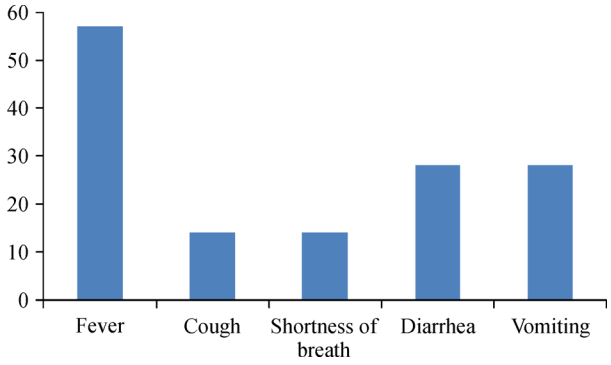


Fig. 1 Graph showing the most common clinical findings (percentage) among the presented pediatric MERS-CoV cases.

Of the seven cases, two (28.6%) cases had platelet counts of $< 150 \times 10^9$/L, and one had an elevated creatinine level due to an underlying ESRD. The rest of the patients had normal blood count, liver function test, and urea and creatinine levels (Table 2). The documented MERS-CoV Ct values were 32–38 for four of the seven cases.

Two (28.6%) patients had abnormal chest radiographic findings of bilateral infiltration (Fig. 2). One (14.3%) required ventilatory support, and two (28.6%) required supplemental oxygen. All the seven patients were discharged without complications.

Table 1 Summary of clinical presentation and outcome of pediatric MERS-CoV cases

Number	Age (years)	Gender	Symptom	Comorbidity	CXR finding	Intensive care unit	Days of illness before hospitalization	Linked to	O_2 requirement
1	16	Male	Fever, SOB, diarrhea, vomiting	ESRD, asthma	Pneumonic infiltration	YES	2	Contact with confirmed case	6 days
2	10	Female	Fever, cough, vomiting, diarrhea	NO	Normal	NO	7	NA	Nil
3	13	Female	Fever	Miliary TB	Bilateral diffuse	NO	2	NA	12 days
4	6	Female	Fever	NO	Normal	NO	1	No	Nil
5	0.75	Male	Asymptomatic	NO	Normal	NO	Asymptomatic	Mother and grandmother confirmed cases	Nil
6	9	Female	Asymptomatic	Sickle cell anemia	Normal	NO	Asymptomatic	NA	Nil
7	1.5	Male	Asymptomatic	NO	Normal	NO	Asymptomatic	Mother confirmed case	Nil

ESRD, end-stage renal disease; NPS, nasopharyngeal swab; POS, positive; SOB, shortness of breath; CXR, chest X-ray; TB, tuberculosis; NA, not available.

Table 2 Laboratory data on presentation of pediatric MERS-CoV cases

Number	Viral Ct value	WBC	Hgb	Plat	Neut count	Neut %	CK	ALT	AST	Creat	Albumin
1	NA	6.1	91	58	4.95	81.0	169	37	91	1256.1	NA
2	37	3.8	149	145	0.18	4.6	NA	NA	NA	NA	34
3	32	3	90	467	2.25	70.6	NA	6	71	44	26
4	36	8.6	138	500	5.14	60.0	NA	NA	NA	NA	41
5	NA	17.9	105	406	1.93	10.8	62	NA	NA	36.3	NA
6	38	13.3	77	352	9.19	69.2	NA	NA	NA	NA	44
7	NA	11	113	383	2.16	19.6	NA	23	42	NA	45

WBC, white blood cell; Hgb, hemoglobin; Plat, platelet; Neut, neutrophil; CK, creatinine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Creat, creatinine; NA, not available.

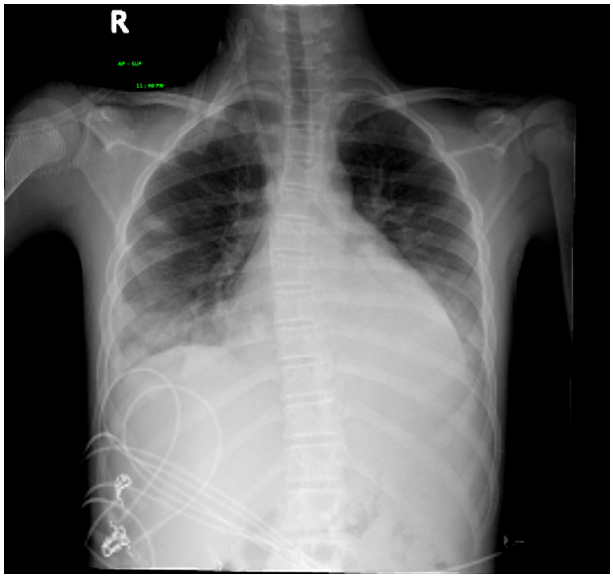


Fig. 2 Portable chest X-ray showing bilateral mid and lower zone patchy air space consolidation with mild right-sided pleural effusion. R, right side.

Discussion

One characteristic feature of MERS-CoV is the extremely low number of children who were affected by the disease. In this report, we found a low rate of pediatric MERS-CoV infection and constituted only 2.4% of all admitted patients to this MERS-CoV referral hospital. The prevalence of MERS-CoV among children and adults was evaluated in two large studies. In a contact screening of 616 children, only nine (1.9%) children were positive compared with 2.2% among 4440 adults ($>$ 17 years of age) [25]. In a second study, children ($<$ 14 years of age) had positive MERS-CoV by PCR test in 10 of 8032 (0.1%) compared with 372 of 48 386 (0.7%) [21]. In adults, the pattern of MERS infection could be sporadic cases, health-care-associated infection or transmission within families [26]. In contrast to infection in adults where health-care-associated infection is predominant [26], most confirmed pediatric cases were related secondary to exposure to other MERS-CoV cases within the same family [17]. The female-to-male ratio in childhood MERS-CoV was 1:1.7 [17], which is not similar to the ratio obtained in this study. The clinical presentation of MERS in adults ranges from asymptomatic to fatal and severe cases [26–28]. By contrast, the course of pediatric MERS cases is usually mild or asymptomatic [17].

Considering that MERS-CoV is a respiratory disease, the most common symptoms in adults were respiratory in nature [26]. In this small case series, fever was the predominant symptom (57%), followed by vomiting (28%), diarrhea (28%), cough (14%), and shortness of breath (14%). Gastrointestinal symptoms were also common manifestations among adult patients [4,26,29].

Variable hematologic and hepatic panel findings were described among adult patients with MERS-CoV and indicated conditions, such as thrombocytopenia and thrombocytosis [30]. In this report, two (28.6%) patients had thrombocytopenia, and the other patients had normal blood count and liver function test. Chronic renal disease was observed in only one patient in the current series, and renal dysfunction was a major pre-existing disease in adults [3]. In this report, all patients were discharged without complications. In the previous review of 31 pediatric cases, the fatality rate was 33.3% [17].

The occurrence of mild diseases in the pediatric age group has no clear explanation. Possible explanations for these findings include low exposure of pediatrics to MERS-CoV, presence of asymptomatic children and mildly symptomatic patients, or the existence of unidentified factors [17]. The manifestation of MERS as asymptomatic or mildly symptomatic may lead to under-detection due to low clinical suspicion. Whether any correlation exists between the occurrence of MERS in children and associated immunological factors is not known. In adults, serologic responses were not detected in asymptomatic infection but were 60%, 93.8%, and 100% in symptomatic

patients without pneumonia, pneumonia without respiratory failure, and with pneumonia and respiratory failure, respectively [31]. For adult patients with MERS-CoV, longer intensive care unit stays and more prolonged virus shedding were associated with $CD4^+$ T-cell responses compared with those of children [32]. In animal model, the development of specific $CD8^+$ T cell and virus-neutralizing antibodies may result in protection against MERS-CoV [33–36]. Thus, children may have a different immunologic response with less $CD4^+$ T-cell responses, resulting in a lower rate of and less severe infection compared with adults. Further studies are needed to better understand pediatric MERS-CoV in terms of clinical presentation, infectivity, and outcome.

Conclusions

MERS-CoV remains an uncommon disease among children, and its course follows a milder path among children than those of adults. Majority of cases were asymptomatic and were diagnosed during the course of contact investigation.

Compliance with ethics guidelines

Sarah H. Alfaraj, Jaffar A. Al-Tawfiq, Talal A. Altuwaijri, and Ziad A. Memish declare no conflict of interest. Ethical board approval is not applicable in this case series. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5).

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