Middle East Respiratory Syndrome Coronavirus Disease in Children

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Background: In the initial description of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, many affected patients were adults with underlying medical comorbidities. Data on the clinical presentation and outcome of pediatric cases are lacking. We report the clinical presentation and outcome of MERS-CoV infection in 11 pediatric patients.

Methods: The clinical presentation, demographic and laboratory data of pediatric patients with MERS-CoV were analyzed.

Results: A total of 11 pediatric cases that tested positive by screening and confirmatory polymerase chain reaction for MERS-CoV were reported from Saudi Arabia. Two patients were symptomatic and the other 9 cases were asymptomatic. The median age of patients was 13 (range 2–16) years. There were 8 females and 3 males (2.7:1 ratio). One symptomatic patient died and the other symptomatic patient recovered. The diagnosis of patients was based on positive nasopharyngeal swabs on 10 patients.

Conclusions: MERS-CoV disease is not limited to adults. Most cases of childhood MERS-CoV infection were asymptomatic and tested positive during contact investigation of older patients. Severe disease can occur in children with underlying conditions.

Key Words: MERS-CoV, Middle East respiratory syndrome coronavirus, coronavirus, pediatric

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Since the emergence of Middle East respiratory syndrome coronavirus (MERS-CoV), the disease affected adults with a high case fatality rate.[1–3] The recent increase in numbers of sporadic cases may have led to a change in the proportion of male and female cases.[4] Up to April 24, 2014, MERS-CoV had caused 254 infections with 93 deaths[5] and most of these cases occurred in the Kingdom of Saudi Arabia (KSA; 287 cases with 85 deaths).[6] Of the initially reported 47 cases in KSA, all patients were adults except for 1 child 14 years of age.[2] A 2-year old child with MERS-CoV was reported from Jeddah, KSA on June 28, 2013,[7] and 3 asymptomatic children <15 years.[2] The disease was associated with a high case fatality rate and recently this rate was observed to be decreasing from 60% to 45%.[3] The initial cases showed disproportionate male predominance.[1,2] And later the proportion of male to female showed a ratio of 1.5.[3] There are no clear data on the clinical presentation and the outcome of pediatric infections with MERS-CoV. We present here the clinical details of the 11 laboratory-confirmed pediatric patients.

We reviewed the clinical records for pediatric patients (0–17 years of age) with laboratory-confirmed MERS-CoV infection who were reported by the Saudi Ministry of Health to World Health Organization from September 1, 2012, to December 2, 2013. The collected data included epidemiologic, demographic, clinical, laboratory and outcome, as described previously.[2] We also grouped the patients as symptomatic or asymptomatic cases based on the presence of fever, cough and shortness of breath or respiratory distress. A confirmed case was defined as any patient who tested positive for MERS-CoV from respiratory specimen using real-time reverse transcriptase polymerase chain reaction (RT amplification of both the upstream E protein (*UpE* gene) and ORF1a for confirmation at –PCR) Saudi Ministry of Health regional laboratory as described previously.[2]

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From September 1, 2012, to December 2, 2013, 11 pediatric patients tested positive for MERS-CoV. Two patients were symptomatic and the other 9 cases were asymptomatic. The median age of patients was 13 (range 2–16) years. There were 8 females and 3 males (2.7:1 ratio).

DESCRIPTION OF SYMPTOMATIC CASES

Case 1

The patient was a 2-year-old boy with cystic fibrosis. He was admitted because of fever and respiratory distress. He had no history of travel, no contact with animals or known MERS-CoV patients. He had no nausea, vomiting and diarrhea. After admission, he was treated with ceftazidime and gentamicin. Sputum culture grew multidrug-resistant *Pseudomonas*. His condition rapidly deteriorated and he was transferred to the intensive care unit. He had tachypnea with intercostal and subcostal recession. Temperature was 37°C, pulse rate of 150/min, respiratory rate 50/min, blood pressure 116/69 mmHg and O_2 saturation 84% (5 L/min O_2). Lungs revealed bilateral diminished air entry with inspiratory fine crepitation and expiratory rhonchi. Heart examination revealed audible 1st and 2nd heart sounds without added murmur. Abdomen was soft, lax with no organomegaly. The patient was electively intubated and started on conventional mechanical ventilation. He was soon switched to high frequency oscillatory ventilation because of worsening respiratory acidosis in spite of escalating conventional support, a routine chest radiograph showed bilateral infiltrate. The patient developed clinical signs of shock with hypoperfusion and hypotension. He was resuscitated with fluid and started on epinephrine infusion. On day 5, he was started on nitric oxide. Nasopharyngeal swab was positive by real-time RTPCR and for H1N1 influenza. The patient had good response in both respiratory and hemodynamic measures. He later developed

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TABLE 1. Clinical, Demographic and Laboratory Characteristics of 6 Pediatric MERS-CoV Infections Reported From KSA

	Sample Source	Age	Gender	Symptoms	Comorbidity	Signs	Sample Type	MERS-CoV PCR Test	Viral Load Ct Value	Imaging	Intensive Care	Treatment Outcome	Follow Up
1	Hospital inpatient	2	Male	Fever, respiratory distress	Cystic fibrosis	Chest: bilateral fine crepitation, ex. ronchi	NPS	+	36	Bilateral diffused infiltrate	+	Death	Death after 2 months
2	Hospital inpatient	14	Female	Fever	Down's syndrome		NPS	+	37	Bilateral diffused infiltrate	No	Discharged home	Well 6 months later
3	Family contact	7	Female	Asymptomatic	None	None	N+T	+	37	ND	No	No	Well 4 months later
4	Family contact	15	Female	Asymptomatic	None	None	NPS	+	35	ND	No	No	Well 6 months later
5	Family contact	14	Male	Asymptomatic	None	None	NPS	+	34	ND	No	No	Well 6 months later
6	Family contact	12	Female	Asymptomatic	None	None	NPS	+	35	ND	No	No	Well 6 months later
7	Family contact	16	Male	Asymptomatic	None	None	NPS	+	36	ND	No	No	Well 6 months later
8	Family contact	7	Female	Asymptomatic	None	None	NPS	+	37	ND	No	No	Well 4 months later
9	Family contact	3	Female	Asymptomatic	None	None	NPS	+	38	ND	No	No	Well 4 months later
10	Contact	13	Female	Asymptomatic	None	None	NPS	+	34	ND	No	No	Well 1 month later
11	Family contact	14	Female	Asymptomatic	None	None	NPS	+	36	ND	No	No	Well 3 months later

NPS, Nasopharyngeal swab; N+T, nasal and tracheal aspirate; ND, not done.

thrombocytopenia with platelet counts of 66–38 (million cells per μL). He also required peritoneal dialysis. The hospital course was complicated by pneumopericardium. On day 16–20, he had repeated episodes of sudden desaturation and CO_2 retention requiring methylprednisone (1 mg/kg/d) therapy. He died 60 days after admission to hospital with respiratory failure and multiorgan failure.

Case 2

The patient was a 14-year-old girl with Down syndrome, repaired ventriculoseptal defect with residual severe mitral regurgitation, history of systolic and diastolic left ventricular impairment and pulmonary hypertension. She was obese (BMI 42.2 kg/m^2) and had hypothyroidism and obstructive sleep apnea, which was managed with home oxygen.

The patient was admitted with cough and fever of 1-day duration. She had no chills, night sweats and symptoms suggestive of upper respiratory tract infection. There was no history of travel or contact with animals. She had no diarrhea and vomiting. Temperature was 39.5°C, respiratory rate 22/min, blood pressure 90/60 mm Hg and heart rate 100/min. Lung auscultation revealed bilateral rhonchi and basilar rales. Heart sounds were distant with a faint systolic murmur. There was lower extremity edema. Chest radiograph showed bilateral infiltrate. Nasopharyngeal swab was positive by real-time RT-PCR for MERS-CoV. Blood cultures were negative and the patient did not have sputum production to warrant culture. She was treated symptomatically and received nebulization treatment, intravenous diuretics, imipenem and oseltamivir. She gradually improved and supplemental oxygen was discontinued. She was discharged home after 7 days and remained in good health.

Asymptomatic Cases

There were 9 asymptomatic pediatric cases. All of these patients except 1 patient were family contacts. They required no hospitalization and had no symptoms or signs of illness (Table 1).

DISCUSSION

We presented a summary of pediatric MERS-CoV infections. No other pediatric cases of MERS-CoV have been reported in the medical literature. This is the first comprehensive report and we attempted to contrast these cases to adult cases. In a recent review of MERS-CoV, the median age of 161 patients was 50 years (14 months to 94 years) and of them 64.5% were male.[4] Although the difference did not reach statistical significance, 73% of index/sporadic cases were male and 60.0% of secondary cases were male.[1–4] By contrast, most of the reported pediatric cases were females. This difference is likely related to the small sample size of the current cases rather than true epidemiological differences.

The 9 asymptomatic pediatric cases were included in the reporting because these cases were positive for 2 specific gene targets (*upE* and *ORF1a*) on rRT-PCR, thus satisfying the World Health Organization case definition. The total asymptomatic cases (adults and children) are increasing and based on a recent publication, it has reached 18 from June to September 2013.[3] These 9 asymptomatic cases had no underlying comorbidities and were detected during routine screening of all contacts of MERS-CoV patients in the community and in the hospitals. It was noted that acute respiratory syndrome coronavirus (SARS-CoV) infections in children <12 years of age was milder and resulted in no mortality.[8] The identification of mild and asymptomatic cases through investigations and testing of contacts of confirmed cases shows that the focus on severe disease as a surveillance strategy may miss significant numbers of mild or asymptomatic cases.[4,9] The detection of these cases was the result of the Saudi Ministry of Health roles in enhanced surveillance and case findings. Identification

of milder and asymptomatic cases results in reduction of the observed CFR.[4] In June 2013, a 2-year-old child was reported from Italy to be MERS-CoV positive. This case was subsequently reclassified as probable case on September 20, 2013.[10] The reclassification was based on the fact that the case did not meet the current World Health Organization case definition for a "confirmed case" for MERS-CoV.[11] An epidemiologic investigation of family contacts in Abu Dhabi also detected an 8-year-old boy with mild respiratory symptoms who acquired the infection in relation to his parents.[12] The child had mild respiratory symptoms, and he was detected from epidemiologic investigation of family contacts. Thus, the total pediatric cases reported are 12 patients. MERS-CoV infection was implicated to cause stillbirth at approximately 5 months of gestation based on the result of positive serologic tests in the mother.[13]

It was observed that MERS-CoV positive patients who died had a higher median age and were male compared with those who recovered or were asymptomatic.[4] In a recent study from Jordan, 474 samples from children <2 years of age tested negative for MERS-CoV by PCR.[14] The negativity of these samples suggests that MERS-CoV was not circulating widely in nearby metropolitan Amman, Jordan, from March 2010 to September 2012.[14] We conclude that MERS-CoV disease is not limited to adults. Most childhood MERS-CoV infection was associated with asymptomatic status discovered during contact investigation of older patients. The screening rate of children revealed a positive rate of 1.12% among 625 screened children.[15] Severe disease tends to occur in children with underlying diseases.

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