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SYSTEMATIC REVIEWS

Middle East respiratory syndrome coronavirus disease is rare in children: An update from Saudi Arabia

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Abstract

AIM

To summarize the reported Middle East respiratory syndrome-coronavirus (MERS-CoV) cases, the associated clinical presentations and the outcomes.

METHODS

We searched the Saudi Ministry of Health website, the World Health Organization website, and the Flutrackr website. We also searched MEDLINE and PubMed for the keywords: Middle East respiratory syndrome-coronavirus, MERS-CoV in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in 2012 to 2016. The retrieved articles were also read to further find other articles. Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary.

RESULTS

From June 2012 to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases. Of these cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. Twenty-five (80.6%) of the cases were reported from the Kingdom of Saudi Arabia. The most common source of infection was household contact (10 of 15 with reported source) and 5 patients acquired infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

CONCLUSION

Utilizing serology for MERS-CoV infection in Jordan and

Saudi Arabia did not reveal any positive patients. Thus, the number of the pediatric MERS-CoV is low; the exact reason for the low prevalence of the disease in children is not known.

Key words: Pediatric; Middle East respiratory syndrome-coronavirus; Children; Respiratory tract infection

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Core tip: The number of the pediatric Middle East respiratory syndrome-coronavirus (MERS-CoV) is low and the exact reason for the low prevalence is not known. A total of 31 pediatric MERS-CoV cases were reported since June 2012. Of all the cases 13 (42%) were asymptomatic and the male to female ratio was 1.7:1. The mean age of patients was 9.8 ± 5.4 years. The most common source of infection was household contact followed by infection within a health care facility. Using real time reverse transcriptase polymerase chain reaction of pediatric patients revealed that 9 out of 552 (1.6%) was positive in the Kingdom of Saudi Arabia.

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INTRODUCTION

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA)^[1]. As more cases were reported, the case fatality rate changed to 40% from 60%^[2-5]. In addition, initially there was a predominance of males; later this ratio decreased^[2,6]. MERS-CoV is characterized by three different patterns of disease: Sporadic cases, intra-familial transmission^[7-9] and health care associated infection^[2,3,10-16]. Despite the increased number overtime and the multiple health care associated outbreaks^[17], the number of pediatric cases remained low during the study period^[18]. The initial description of 47 cases included only a 14-year-old child^[4]. The first pediatric case was a 2-year-old child reported from Jeddah, KSA on June 28, 2013^[19]. Later an additional three asymptomatic children were reported^[4]. The largest report of childhood MERS-CoV cases included eleven, of which two patients were symptomatic and nine were asymptomatic^[18]. The exact reason for this low prevalence of the disease in children is not known. In this study, we summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

MATERIALS AND METHODS

We searched the Saudi Ministry of Health website^[20],

the World Health Organization website^[21], the Flutrackr website^[22], the medical literature and the retrieved published studies for any childhood MERS-CoV infections. We searched MEDLINE and PubMed for the keywords Middle East respiratory syndrome-coronavirus, MERS-CoV, in combination with pediatric, children, childhood, infancy and pregnancy from the initial discovery of the virus in June 2012 until April 19, 2016. The retrieved articles were also read to find other relevant articles.

Statistical analysis

Relevant data were placed into an excel sheet and analyzed accordingly. Descriptive analytic statistics were used in the final analysis as deemed necessary, including mean and standard deviation when applicable and frequency. The statistical review of the study was performed by a biomedical statistician. Statistical review is performed before the submission of the manuscript.

RESULTS

Summary of pediatric cases

From June 2012, to April 19, 2016, there were a total of 31 pediatric MERS-CoV cases as shown in Table 1. Of all the cases, thirteen (13) or 42% were asymptomatic, and there were 17 males, 10 females and 4 unreported (a male to female ratio of 1.7:1). The mean age of patients was $9.8 + 5.4$ (0.75-17) years. Twenty-five cases (80.6%) were reported from KSA; the other patients were in Jordan, United Arab Emirates and the Republic of Korea (Table 1). The most common source of the infection was household contact (10 of 15 with reported source), and 5 patients acquired the infection within a health care facility. About one half of the cases were reported in 2014, and 29% were reported in 2013 and 22.6% in 2015 (Table 2).

Screening of pediatric patients for MERS-CoV

Screening of pediatric patients for MERS-CoV infection using real time reverse transcriptase polymerase chain reaction showed that only 9 out of 552 (1.6%) were positive in KSA^[23]. However, serologic testing of pediatric patients admitted with lower respiratory tract infection in Jordan and Saudi Arabia revealed no positive tests^[24,25] (Table 3).

Pregnancy associated MERS-COV

The effect of MERS-CoV infection on the fetus was described in eight cases^[26-29] as summarized in Table 4. The mean age of the mothers was $32.25 + 3.4$ years, and the mean gestational age was $28.4 + 6.3$ wk. Death of the fetus was observed in 3 (37.5%) of the 8 fetuses.

DISCUSSION

Despite the total number of MERS cases increasing, especially in KSA, the number of pediatric cases remained low during the study period. Initially, the

Table 1 Summary of reported pediatric Middle East respiratory syndrome cases

Age	Gender	Country	Sample source	Year of reporting	Symptoms	Co-morbidity	Signs	Sample type	Viral load ct value	Imaging	Intensive care	Death	Ref.
2	Male	KSA	Hospital inpatient	2013	Fever, respiratory distress	Cystic fibrosis	Chest: Bilateral fine creptitation	NPS	36	Bilateral diffused infiltrate	+	Yes	[18]
14	Female	KSA	Hospital inpatient	2013	Fever	Down's syndrome	None	NPS	37	Bilateral diffused infiltrate	No	No	[18]
7	Female	KSA	Family contact	2013	Asymptomatic	None	None	N + T	37	ND	No	No	[18]
15	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
14	Male	KSA	Family contact	2014	Asymptomatic	None	None	NPS	34	ND	No	No	[18]
12	Female	KSA	Family contact	2014	Asymptomatic	None	None	NPS	35	ND	No	No	[18]
16	male	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
7	Female	KSA	Family contact	2014	Asymptomatic	None	none	NPS	37	ND	No	No	[18]
3	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	38	ND	No	No	[18]
13	Female	KSA	Contact	2014	Asymptomatic	None	none	NPS	34	ND	No	No	[18]
14	Female	KSA	Family contact	2013	Asymptomatic	None	none	NPS	36	ND	No	No	[18]
0.75	Male	KSA	Not known	2014	ICU	Nephrotic syndrome	Respiratory distress	Tracheal aspirate	NA	Diffuse bilateral haziness	Yes	Yes	[35]
4	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA	NA	NA	ND	No	No	[36]
8	Male	KSA	NA	2013	Mild respiratory symptoms	None	NA	NA	NA	ND	NA	No	[37]
17	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
11	NA	KSA	Contact	2014	Asymptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
16	NA	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
13	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
10	M	KSA	Hospital contact	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
2	NA	KSA	NA	2014	Symptomatic	Congenital anomalies	NA	NA	NA	NA	NA	NA	[20,22]
11	M	KSA	Hospital contact	2014	Symptomatic	Brain tumor	NA	NA	NA	NA	NA	NA	[20,22]
17	M	KSA	NA	2014	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	South Korea	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[22]
2	M	KSA	Hospital contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
16	M	KSA	contact	2015	Symptomatic	NA	NA	NA	NA	NA	NA	NA	[20,22]
7	F	Jordan	Contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]
0.8	F	Jordan	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[22]
14	M	KSA	Contact	2015	Symptomatic	None	NA	NA	NA	NA	NA	NA	[20,22]
4	M	UAE	NA	2014	NA	NA	NA	NA	NA	NA	NA	NA	[22]
8	M	UAE	Family contact	2013	NA	NA	NA	NA	NA	NA	NA	NA	[22]
11	M	UAE	Family contact	2015	Asymptomatic	None	NA	NA	NA	NA	NA	NA	[22]

NPS: Nasopharyngeal swab; N + T: Nasal and tracheal aspirate; ND: Not done; KSA: Kingdom of Saudi Arabia; UAE: United Arab Emirates; ICU: Intensive care unit; NA: Not available.

testing in KSA was directed towards hospitalized patients with severe pneumonia. In 2015, the Saudi Ministry of Health added a specific case definition for MERS-CoV infection in children^[30]. The definition includes those \leq 14 years, meets the adult case definition and has either a history of exposure to a confirmed or suspected MERS-CoV in the preceding 14 d or a history of contact with camels or camel products in the preceding 14 d^[30]. The case definition also includes children with unexplained severe pneumonia^[30]. The 2015 change in the case definition does not account for the low rate of childhood MERS-CoV infection as 33% of the cases were reported in 2014 before the case definition was changed. One of the reasons for an increased number of cases in 2014 during the Jeddah outbreak was increased testing of asymptomatic and mildly symptomatic patients^[11].

Table 2 Summary of the demographic characteristics of pediatric Middle East respiratory syndrome-coronavirus

	No.	%
Male:female	17:10 (1.7:1)	63 vs 37
Saudi	20	83.3
City		
Jeddah	7	29.2
Riyadh	7	29.2
Hafr al-Batin	3	12.5
Symptomatic	12	50.0
Death	8	33.3
Year of report		
2013	9	29
2014	15	48.4
2015	7	22.6

Table 3 Summary of different studies examining Middle East respiratory syndrome-coronavirus infection in children

Country	Testing method	Population	Positive n (%)	Yr	Ref.
KSA	rRT-PCR	Screening of children	9/552 (1.6)		[23]
KSA	Neutralizing antibodies testing	Serum samples from children hospitalized for lower respiratory tract infections	0/158 (0)	May 2010-May 2011	[25]
Jordan	rRT-PCR	Hospitalized children < 2 yr of age	0/2427 (0)		[24]

rRT-PCR: Real time reverse transcriptase polymerase chain reaction; KSA: Kingdom of Saudi Arabia.

The pattern of MERS-CoV pediatric cases was similar to the 2003 SARS outbreak. Children were less affected than adults and children less than 2 years of age had milder disease^[31]. In the largest screening of contacts, the rate of MERS-CoV positive children (1.6%, 9/616) compared to 2.2% (99/4440) in adults ($P = 0.23$)^[23]. Thus, in this study utilizing MERS-CoV PCR the positivity rate did not differ in children and adults.

In adults with MERS-CoV infections, three patterns of transmissions were observed: Sporadic (primary) cases presumed to be due to animal exposure (mainly camels), household contacts or health care associated infections^[32]. In KSA, the majority (45%) of cases were health care-associated infections, 38% were primary cases, and 13% were household contacts^[32]. In contrast, in the majority of pediatric cases that reported source of acquisition (66.7% of the 15 with reported source), the disease was acquired through household contact. This pattern indicates a low exposure of children to animals and a higher rate of health care associated infections in adult wards. The male to female ratio (2.8:1 and 3.3:1) was initially high^[3,4]. This apparent male predominance could be explained by the nature of hospital outbreaks^[2]. Eventually the male to female ratio was reduced to 1.3:1

Table 4 Summary of pregnancy associated Middle East respiratory syndrome-coronavirus infection

Age of the patient (yr)	Gestational age	Fetal outcome	Diagnostic test	Country	Ref.
39	5 mo	Still birth	Antibody by EIA	Jordan	[26]
33	32 wk	Healthy infant	PCR	Saudi Arabia	[27]
32	32 wk	Healthy	PCR	United Arab Emirates	[28]
34	34 wk	Died	PCR	Saudi Arabia	[29]
32	38 wk	Survived	PCR	Saudi Arabia	[29]
31	24 wk	Died	PCR	Saudi Arabia	[29]
27	22 wk	Survived	PCR	Saudi Arabia	[29]
30	23 wk	Survived	PCR	Saudi Arabia	[29]

PCR: Polymerase chain reaction; EIA: Enzyme immunoassay.

to 1.8:1^[5,6]. Consistent with these studies, the male to female ratio in children with MERS-CoV was 1.7:1 and may indicate similar exposure of children to index cases in the household settings and differential host factors.

Possible explanations for the lower number of pediatric cases compared to adults include differential testing of adult patients and milder diseases in children; although, serologic testing of pediatric patients in KSA and Jordan did not reveal any positive cases^[24,25]. In the largest sero-epidemiologic survey in KSA, the study did not include children and thus it is difficult to establish the rate of sero-positivity in children^[31].

The MERS-CoV infection rate in children remains low and possible explanations include: A milder disease in children, asymptomatic infection, or the presence of yet to be identified factors. The development of a shorter duration of MERS in children is another possible explanation. If this is the case, it may limit the development of a positive serology. In one study, delayed antibody responses as measured with the neutralization test was associated with severe diseases^[33]. The longevity of antibodies in MERS-CoV cases might be limited as was the case with SARS^[33,34]. The only study of serology among children was done among hospitalized pediatric cases who presented with lower respiratory tract infections^[25]. There is no systematic screening of exposed children using serologic testing; this limited the interpretation of available serologic studies.

Little data also exist regarding the effect and the likelihood of MERS-CoV in pregnancy. Eight cases were reported^[26,27,29]. The outcome was favorable in the majority of cases. The exact prevalence of MERS-CoV antibodies and exposure of pregnant women to MERS-CoV is not known.

In conclusion, the number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add

to the understanding of the low prevalence in this age group.

COMMENTS

Background

Middle East respiratory syndrome-coronavirus (MERS-CoV) was first isolated in 2012 from a patient in the Kingdom of Saudi Arabia (KSA). Despite the increased number of MERS-CoV cases overtime, the number of pediatric cases remained low. The exact reason for this low prevalence of the disease in children is not known. The aim of this study is to summarize the reported MERS-CoV cases and the associated clinical presentation and the outcome.

Research frontiers

The first pediatric case was a two-year-old child reported from Jeddah, KSA on June 28, 2013. Later an additional three asymptomatic children were reported. The largest report of childhood MERS-CoV cases included eleven, including nine asymptomatic cases.

Innovations and breakthroughs

The number of MERS-CoV infections in pediatric patients remains low. Possible explanations include low exposure, presence of asymptomatic, mildly symptomatic patients or the presence of yet to be identified factors. The immune system predisposing to severe disease and to fatal outcome remains unknown. An exploration of the virus-host interaction may add to the understanding of the low prevalence in this age group.

Applications

Despite the low number of pediatric MERS-CoV cases, it is important to continue to monitor the development of this disease in this age group and to understand the risk factors.

Terminology

MERS-CoV is a new emerging virus that was first isolated in 2012.

Peer-review

This complication of all known pediatric cases is a useful contribution to the medical literature, and knowing it is possible but rare is important.

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