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Postnatally Acquired Zika Virus Disease Among Children, United States, 2016–2017

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Abstract

Background.—The clinical findings among children with postnatally acquired Zika virus disease are not well characterized. We describe and compare clinical signs and symptoms for children aged <18 years.

Methods.—Zika virus disease cases were included if they met the national surveillance case definition, had illness onset in 2016 or 2017, resided in a participating state, and were reported to the Centers for Disease Control and Prevention. Pediatric cases were aged <18 years; congenital and perinatal infections were excluded. Pediatric cases were matched to adult cases (18−49 years). Clinical information was compared between younger and older pediatric cases and between children and adults.

Results.—A total of 141 pediatric Zika virus disease cases were identified; none experienced neurologic disease. Overall, 28 (20%) were treated in an emergency department, 1 (<1%) was

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hospitalized; none died. Of the 4 primary clinical signs and symptoms associated with Zika virus disease, 133 (94%) children had rash, 104 (74%) fever, 67 (48%) arthralgia, and 51 (36%) conjunctivitis. Fever, arthralgia, and myalgia were more common in older children (12−17 years) than younger children (1−11 years). Arthralgia, arthritis, edema, and myalgia were more common in adults compared to children.

Conclusions.—This report supports previous findings that Zika virus disease is generally mild in children. The most common symptoms are similar to other childhood infections, and clinical findings and outcomes are similar to those in adults. Healthcare providers should consider a diagnosis of Zika virus infection in children with fever, rash, arthralgia, or conjunctivitis, who reside in or have traveled to an area where Zika virus transmission is occurring.

Keywords

pediatric; Zika; epidemiology

Zika virus is a mosquito-borne flavivirus primarily transmitted to humans by *Aedes (Stegomyia)* species mosquitoes. Zika virus also can be transmitted congenitally, perinatally from a viremic mother to her newborn, sexually, and through blood trans-fusion or laboratory exposure. Most Zika virus infections are asymptomatic. Clinical illness, when it occurs, is generally mild and characterized by acute onset of fever, maculopapular rash, arthralgia, and/or nonpurulent conjunctivitis [1]. However, Guillain-Barré syndrome, other neurologic manifestations (eg, meningoencephalitis, myelitis, and uveitis), and thrombocytopenia have rarely been reported following Zika virus infections in adults [2–4]. Congenital Zika virus infections can cause fetal loss as well as microcephaly and other serious neurologic manifestations (eg, corpus callosum agenesis, optic nerve hypoplasia, hearing loss). The specific clinical findings and outcomes of postnatally acquired Zika virus disease among children are not well described [5–7]. We describe the clinical manifestations and outcomes among children aged <18 years with postnatally acquired Zika virus disease and compare the clinical findings of children of different age groups, and between children and adults.

METHODS

Zika virus disease became a nationally notifiable condition in 2016. State and territorial health departments report cases to the Centers for Disease Control and Prevention (CDC) via ArboNET, the national arboviral disease surveillance system. Zika virus disease cases reported to ArboNET were eligible for inclusion in this analysis if they (1) met the national surveillance case definition for confirmed or probable disease [8]; (2) had illness onset in 2016 or 2017; and (3) were residents of 1 of 10 participating states (California, Indiana, Maryland, Massachusetts, Minnesota, New Jersey, New York [exclusive of New York City], Pennsylvania, Texas, or Virginia). A pediatric case was defined as a child aged <18 years at the time of illness onset; congenital and perinatal infections were excluded. A Zika virus disease case that met the 3 eligibility criteria but occurred in an adult (aged 18−49 years) was matched to each pediatric case based on state of residence, pregnancy status, and case status (ie, confirmed or probable). If an adult case could not be identified within the

pediatric case's state of residence, one was identified from another of the participating states.

As part of routine public health surveillance for Zika virus disease, health department personnel obtained demographic, clinical, and laboratory data from medical records, healthcare providers, and patients/guardians. Deidentified data were collected and managed using a secure, web-based application (REDCap) hosted at CDC [9]. Categorical variables are presented by frequency distribution (eg, frequency counts and percentages). Clinical information and outcomes of younger and older pediatric cases were compared using Fisher exact test or χ^2 test. Characteristics of pediatric cases were compared to matched adult cases using conditional logistic regression. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Overall, 141 pediatric cases of Zika virus disease meeting the study inclusion criteria were reported from the participating states. One (<1%) case-patient was an infant aged <1 year, 7 (5%) were aged 1–4 years, 43 (30%) were aged 5–11 years, and 90 (64%) were aged 12–17 years. Of the 141 case-patients, 90 (64%) were female, and 11 were pregnant (age range 14–17 years). Ten children were reported to have comorbidities, including asthma (7 patients), asthma and eczema (N = 1), asthma and history of seizures (N = 1), and history of cancer (N = 1). Two (1%) patients were infected in their home state of Texas via local mosquito-borne transmission. The remaining 139 (99%) patients acquired Zika virus infection during travel to a country or territory outside of the continental United States. The most common travel destinations were Mexico (N = 28 patients), the Dominican Republic (N = 26), and Puerto Rico (N = 22). Of the 141 case-patients, 125 (89%) met the laboratory criteria for a confirmed case, including 109 (87%) positive for Zika virus RNA by reverse transcription polymerase chain reaction, and 16 (13%) positive for Zika virus immunoglobulin M (IgM) and neutralizing antibodies and negative for dengue virus neutralizing antibodies. Sixteen case-patients met the laboratory criteria for a probable case, including 11 (69%) positive for Zika virus IgM with neutralizing antibodies against both Zika and dengue viruses, and 5 (31%) positive for Zika virus IgM and neutralizing antibodies, negative dengue virus IgM, and no dengue neutralizing antibody testing performed.

No children were reported to have neurologic signs or symptoms consistent with meningitis, encephalitis, or Guillain-Barré syndrome. Of the 4 primary clinical signs and symptoms associated with Zika virus disease, 133 (94%) children had rash, 104 (74%) fever, 67 (48%) arthralgia, and 51 (36%) conjunctivitis. Overall, 116 (82%) children had ≥2 of these 4 signs and symptoms, including 99 (70%) with both fever and rash; 73 (52%) had ≥3, and 26 (18%) had all 4. Only 2 (1%) patients did not have a fever or rash. A description of the rash was available for 65 (49%) of 133 children with rash. Of those, 61 (94%) were described as maculopapular; 32 (49%) were described as pruritic. Most rashes were reported to have a diffuse distribution, but some were limited to a single area of the body, most often the face or torso. Gastrointestinal symptoms (ie, nausea, vomiting, diarrhea, abdominal pain) and respiratory symptoms (ie, sore throat, cough) were reported in 38 (27%) and 37 (26%) of patients, respectively. Of the 15 patients with cough, 1 had a history of asthma. Of the 28

pediatric case-patients that had a complete blood count (CBC) performed, 14 (50%) were reported to have leukopenia (ie, white blood cell count <5000 cells/μL), with nadir values ranging from 2700 to 4400 mm^3. None were reported to have thrombocytopenia (ie, platelets <150 000 cells/mL). Overall, 28 (20%) patients with a median age of 9.5 years (range 4–17 years) were treated in an emergency department. One (<1%) child was hospitalized for 3 days because of fever, cough, and poor oral intake. None of the pediatric case-patients died.

Clinical presentations were compared for children aged 1–11 years and those aged 12–17 years (Table 1); the single infant (11 months of age) was excluded from this part of the analysis. The infant was reported to have fever, maculopapular rash, diarrhea, and vomiting, and was not hospitalized or treated in an emergency department. Thirty-eight (76%) case-patients aged 1−11 years were female compared to 51 (57%) of those aged 12–17 years (P = .03). Younger children were more likely to be treated in an emergency room (31%) than older children (13%; P = .01). The most common symptom among all ages was rash occurring in >90% of patients of both age groups. A description of the rash was available for 26 children aged <12 and for 39 children aged ≥12 years. Twenty-three (88%) of 26 children aged <12 years had a maculopapular rash, compared to 38 (97%) of 39 children aged ≥12 years (P = .29). Eleven of 26 (42%) children aged <12 years had a pruritic rash, compared to 21 (54%) of 39 children aged ≥12 years (P = .36). The only symptoms that were significantly different between younger and older children were fever, arthralgia, and myalgia, all of which were more common in older children (Table 1).

When comparing children to adults with Zika virus disease, there were no differences in the proportion of patients who were female, presented to an emergency department, or were hospitalized (Table 2). Arthralgia, arthritis, edema, and myalgia were significantly more common in adults. However, when the frequency of these findings were compared between the 2 groups of children (ie, aged 1−11 years and 12−17 years) and their respective matched adults, the differences in arthralgia, arthritis, and myalgia only remained significant for the younger children. Edema was significantly more common in adults compared to older children (aged 12−17 years), and there were no cases of edema in younger children for comparison. Among the adult cases, a description of the rash was available for 62 (46%) of 134 adults with rash. Similar to what was reported among children, 55 (89%) of the rashes in adults were described as maculopapular and 30 (48%) were described as pruritic.

DISCUSSION

This report of 141 children with postnatally acquired Zika virus disease supports previously published case series that reported the clinical presentation in children to be generally mild [5–7]. Although our study may not have included enough children to detect very rare presentations, our findings support previous reports that neurologic presentations are uncommon in this age group [7–11]. Signs and symptoms experienced by most pediatric patients included rash, fever, and headache. Almost two-thirds of patients were female; notably, this difference was most evident among children aged 1−11 years and did not necessarily result from increased testing among adolescent girls of reproductive age.

Of the 4 characteristic clinical signs and symptoms of Zika virus disease, rash was the most commonly reported, followed by fever, arthralgia, and conjunctivitis. The characteristics of the rash among these cases are consistent with common viral exanthema and therefore cannot be used to differentiate Zika virus infection from other infectious causes. Fever, the second most frequently reported symptom, was more common in older children; potential reasons for this difference are unknown. The proportions of children with rash, arthralgia, or conjunctivitis were generally higher in this report compared to previously published case series, including 1 report by Goodman et al that contained some of the cases included here [5–7, 11]. One explanation for this difference is that the cases described here, though identified through passive surveillance, were investigated further to improve data completeness and quality. Additionally, the patients described in this report met a standard national surveillance case definition, which included clinical, epidemiologic, and laboratory criteria. In contrast, some of the previous reports used different inclusion criteria (eg, requiring fever, evaluation in an emergency room, or hospitalization) or did not include laboratory evidence of Zika virus infection [7, 10, 11].

In initial case reports of pediatric Zika virus disease, 7 of 10 identified patients presented with gastrointestinal symptoms, prompting speculation that these symptoms might occur more frequently in children compared to adults [5]. Subsequent descriptions of pediatric patients with Zika virus infection did not assess the frequency of gastrointestinal symptoms [6, 7]. Gastrointestinal symptoms were not a prominent finding among our larger cohort of patients, and there were no differences in the frequency of occurrence between children and adults. A recent case report noted mesenteric adenitis associated with abdominal pain in a child with Zika virus infection [12]. Although 10% of the children in our series reported abdominal pain, this is a nonspecific finding that could be due to several factors, and only 5% had evidence of peripheral lymphadenopathy.

Upper respiratory infection symptoms, such as cough or rhinorrhea, were more commonly reported (37–50% of cases with these symptoms) in 2 previous case series [7, 10]. However, both of these studies only included cases that were hospitalized or treated in an emergency department. Additionally, the difference could be related to coinfections with other respiratory pathogens for which patients were not screened. Among the cohort of pediatric patients treated in an emergency department in Puerto Rico, 69 (20%) reported preexisting asthma [7]. Asthma was also a common comorbidity in our cohort but did not appear to be associated with reports of respiratory symptoms; only 1 of the 15 patients presenting with cough had a history of asthma.

Leukopenia was previously reported in 33% (4/12) of a small cohort of children hospitalized with Zika virus infection in Singapore [10]. In our study, half (14/28) of the children who had a CBC performed had evidence of leukopenia. However, 20% of the 141 children identified had a CBC performed, and we do not know if these results were representative of the larger population.

In general, the signs and symptoms of Zika virus disease in children are similar to many other diseases, such as chikungunya, dengue, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsiosis, and group A streptococcal infections. However, there are a few

clinical features that appear to be more prominent with the diseases that would be in the differential specifically for an ill child who was exposed to mosquitoes in an area where Zika virus was circulating. For example, arthralgia appears to be more common among children with chikungunya and thrombocytopenia may be more common among those with dengue [13–15]. However, because dengue and chikungunya virus infections share a similar geographic distribution and symptomology with Zika virus infection, children with suspected Zika virus infection should be evaluated and managed for possible dengue or chikungunya virus infection until the etiologic agent can be identified through laboratory testing.

To our knowledge, this is the first study to compare characteristics of Zika virus disease between children and matched adults. We found that signs and symptoms among pediatric and adult patients were similar with the exception of arthralgia, arthritis, myalgia, and edema which were more common in adults. Notably, arthralgia and myalgia were also more common in older children than in younger children. Higher proportions of arthralgia and myalgia were previously observed among older children compared to younger children in Puerto Rico [6]. Because these symptoms are not visibly apparent, these differences may be related to inability of young children to describe these subjective symptoms as opposed to true differences in disease presentation.

This analysis is subject to several limitations. Due to limited numbers of cases in children aged <1 year, we were unable to describe this group specifically. We included only symptomatic cases reported to CDC that met the national confirmed or probable case definition, which might not be representative of all Zika virus disease in children. There likely were other cases of pediatric Zika virus disease during the time period under study that were not identified by passive surveillance because the patients did not seek care or were not tested for evidence of recent Zika virus disease and did not receive a diagnosis. Finally, the data presented here are from 10 states and may not be representative of all cases nationally; however, they represent roughly 35% of the 411 pediatric cases reported in the continental United States during the study period (CDC unpublished). Furthermore, a previous case series of all cases reported nationally and a series of cases identified in Florida reported similar findings among children suggesting these data may be fairly representative [16].

The symptoms frequently reported among children with Zika virus disease are common to many childhood illnesses and are not notably different than those experienced by adults. Healthcare providers should consider Zika virus disease in the differential diagnosis for children with acute onset of fever, rash, arthralgia, or conjunctivitis, who reside in or traveled to an area with active Zika virus transmission. Although Zika virus disease appears to be a mild illness in children, healthcare providers should report suspected cases to their state or local health department to facilitate diagnosis and mitigate the risk for local transmission.

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Table 1.

Characteristics of Postnatally Acquired Zika Virus Disease Among Children by Age Group[a]

	1–11 years (N = 50)		12–17 years (N = 90)		
Characteristic	**No.**	**(%)**	**No.**	**(%)**	***P*Value**
Female	38	(76)	51	(57)	.02
Emergency room	16	(32)	12	(13)	<.01
Hospitalized	1	(2)	0	(0)	.36
Signs and symptoms					
Rash	49	(98)	83	(92)	.26
Fever	31	(62)	72	(80)	.02
Headache	21	(42)	49	(54)	.16
Arthralgia	15	(30)	52	(58)	<.01
Myalgia	14	(28)	41	(46)	.04
Conjunctivitis	20	(40)	31	(34)	.51
Sore throat	6	(12)	22	(24)	.08
Nausea/vomiting	6	(12)	17	(19)	.29
Diarrhea	5	(10)	12	(13)	.56
Cough	6	(12)	8	(9)	.56
Abdominal pain	5	(10)	9	(10)	1.00
Arthritis	2	(4)	5	(6)	1.00
Lymphadenopathy	2	(4)	5	(6)	1.00
Stiff neck	1	(2)	3	(3)	1.00
Oral ulcer	1	(2)	3	(3)	1.00
Edema	0	(0)	2	(2)	.54

[a]Excludes 1 infant.

Table 2.

Characteristics of Postnatally Acquired Zika Virus Disease Among Children and Adults

	Children[a] (N = 140)		Adults (N = 140)				
Characteristic	**No.**	**(%)**	**No.**	**(%)**	**OR**	**(95% CI)**	***P*Value**
Female	89	(64)	88	(63)	0.97	(0.58–1.60)	.90
Emergency room	28	(20)	26	(18)	1.10	(0.60–2.02)	.76
Hospitalized	1	(1)	3	(2)	0.33	(0.04–3.21)	.34
Signs and symptoms							
Rash	132	(94)	134	(96)	0.75	(0.26–2.16)	.59
Fever	103	(74)	108	(77)	0.81	(0.45–1.44)	.47
Headache	70	(50)	79	(56)	0.74	(0.45–1.23)	.25
Arthralgia	67	(48)	97	(69)	0.43	(0.27–0.71)	<.01
Myalgia	55	(39)	79	(56)	0.52	(0.32–0.84)	.01
Conjunctivitis	51	(36)	62	(44)	0.69	(0.42–1.16)	.16
Sore throat	28	(20)	17	(12)	1.92	(0.95–3.85)	.07
Nausea/vomiting	23	(16)	18	(13)	1.36	(0.68–2.71)	.39
Diarrhea	17	(12)	22	(16)	0.71	(0.34–1.48)	.36
Abdominal pain	14	(10)	7	(5)	2.40	(0.85–6.81)	.10
Cough	14	(10)	11	(8)	1.30	(0.57–2.97)	.53
Arthritis	7	(5)	16	(11)	0.36	(0.13–0.99)	.05
Lymphadenopathy	7	(5)	11	(8)	0.64	(0.25–1.64)	.35
Stiff neck	4	(3)	6	(4)	0.67	(0.19–2.36)	.53
Oral ulcer	4	(3)	5	(4)	0.75	(0.17–3.35)	.71
Edema	2	(1)	12	(9)	0.17	(0.04–0.75)	.02

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Excludes 1 infant.