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*Pediatrics* 2010;125;e787; originally published online March 1, 2010;
DOI: 10.1542/peds.2009-1488

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http://pediatrics.aappublications.org/content/125/4/e787.full.html

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Generalized Petechial Rashes in Children During a Parvovirus B19 Outbreak

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KEYWORDS: parvovirus, epidemiology

ABBRERATIONS:
IgM: immunoglobulin M
IgG: immunoglobulin G
PCR: polymerase chain reaction
GAS: group A beta-hemolytic Streptococcus
www.pediatrics.org/cgi/doi/10.1542/peds.2009-1488
doi:10.1542/peds.2009-1488
Accepted for publication Oct 29, 2009
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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1088-4275)
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

WHAT'S KNOWN ON THIS SUBJECT: Reports about petechial or purpuric rashes that are associated with acute parvovirus B19 infection usually describe only sporadic cases with distinctively focal (eg, glove and sock) rash distributions.

WHAT THIS STUDY ADDS: During a community outbreak of fifth disease, parvovirus proved to be a common cause of generalized petechial rash in children. Associated fever, leukopenia, and serologic tests link this rash to the viremic phase of infection.

abstract

OBJECTIVES: Human parvovirus B19 infection is associated not only with erythema infectiosum (fifth disease) but also, rarely, with purpuric or petechial rashes. Most reports of these atypical rashes describe sporadic cases with skin lesions that have distinctively focal distributions. During a community outbreak of fifth disease, we investigated a cluster of illnesses in children with generalized petechial rashes to determine whether parvovirus was the causative agent and, if so, to describe more fully the clinical spectrum of petechial rashes that are associated with this virus.

METHODS: Systematic evaluation was conducted by general pediatricians of children with petechial rashes for evidence of acute parvovirus infection.

RESULTS: During the outbreak, acute parvovirus infection was confirmed in 13 (76%) of 17 children who were evaluated for petechial rash. Confirmed case patients typically had mild constitutional symptoms, and most (11 [85%] of 13) had fever. Petechiae were typically dense and widely distributed; sometimes accentuated in the distal extremities, axillae, or groin; and usually absent from the head/neck. Most confirmed case patients had leukopenia, and several had thrombocytopenia. Parvovirus immunoglobulin M was detected in 8 (73%) of 11 acute-phase serum specimens, and immunoglobulin G was detectable only in convalescent specimens. Parvovirus DNA was detected in all 7 tested serum specimens, including 2 acute-phase specimens that were immunoglobulin M negative. All case patients had brief, uncomplicated illnesses, but 6 were briefly hospitalized and 1 underwent a bone marrow examination. Two case patients developed erythema infectiosum during convalescence.

CONCLUSIONS: During an outbreak of fifth disease, parvovirus proved to be a common cause of petechial rash in children, and this rash was typically more generalized than described in case reports. Associated clinical features, hematologic abnormalities, and serologic test results are consistent with viremia-associated illness that is distinct from and occasionally followed by erythema infectiosum. Pediatrics 2010; 125:e787-e792
In addition to erythema infectiosum (fifth disease), acute infection with human parvovirus B19 can be associated with purpuric or petechial rashes. These parvovirus-associated hemorrhagic rashes seem to be uncommon, and published reports have described only solitary or sporadic cases (reviewed by McNeeley et al. and additionally reported by others). Most case reports emphasized the distinctively focal (gloves and socks, bathing trunk, or acropetechial) distribution of these atypical rashes, and only a few reports have described generalized petechial rashes associated with parvovirus infection. We could find no description of an outbreak of parvovirus-associated petechial rash in the English-language medical literature.

During a recent community outbreak of fifth disease, we obtained serologic confirmation of acute parvovirus infection in a 13-year-old boy with an index case of fever, generalized petechial rash, and neutropenia. After confirming parvovirus infection in a second child with a similar illness, we instituted prospective case finding in our network of pediatric practices and began to evaluate systematically petechial rash illnesses for evidence of parvovirus infection. Our objectives were first, to determine whether additional cases of parvovirus-associated petechial rash illness might be occurring during the fifth disease outbreak and, then, to describe more fully the spectrum of clinical and laboratory features of this infrequently reported illness.

METHODS

In early March 2007, we sent a short e-mail description of the index case to all 32 of our pediatricians who are associated with UW Health, a network of medical providers that are affiliated with the University of Wisconsin in south central Wisconsin. To encourage case finding, network pediatricians were alerted to the possibility of relationship between petechial rashes and parvovirus B19 infection, asked to watch for any suspected case defined as a petechial rash of unknown cause in a child, and informed about procedures for serologic and virologic testing for parvovirus infection. Throughout the remainder of winter and spring, network pediatricians received e-mail updates about the outbreak investigation and were encouraged to obtain parvovirus tests in suspected cases.

A confirmed case of parvovirus-associated petechial rash was defined as an otherwise unexplained petechial rash in a child for whom laboratory evidence of acute parvovirus B19 infection or, when no serum specimen was available for testing, a temporal linkage to an illness consistent with erythema infectiosum (transient slapped cheek appearance followed by a reticular rash on the extremities). Laboratory evidence of acute parvovirus infection was defined as any of the following: (1) detectable parvovirus-specific immunoglobulin M (IgM) antibody in an acute or convalescent serum specimen; (2) specific immunoglobulin G (IgG) antibody seroconversion in paired specimens; or (3) positive polymerase chain reaction (PCR).

Serologic tests for IgM- and IgG-specific parvovirus B19 antibodies were performed in the reference laboratories that routinely provide serologic testing services to UW Health. The Wisconsin State Laboratory of Hygiene (Madison, WI) used an indirect fluorescent antibody assay (Biokin, Dublin, Ireland), and the ARUP Laboratories (Salt Lake City, UT) used an enzyme-linked immunosorbent assay (Biokin). Serum testing for parvovirus B19 DNA was performed by PCR using 2 primers directed at the VPI gene.

To place confirmed cases in epidemiologic context, we used administrative data from the 2 reference laboratories to calculate both the number of parvovirus B19 IgM antibody tests ordered by UW Health providers and the number of tests that were positive during each quarter of the outbreak year (2007) and the 3 preceding years (2004-2006).

Clinical data and laboratory test results from all confirmed cases were obtained by retrospective medical chart review and by interviews with providers and patient families. Written consent for study participation was obtained from the families of all case patients, in accordance with a study protocol that was approved by the Health Sciences Human Subjects Committee of the University of Wisconsin-Madison.

RESULTS

Network pediatricians reported 17 suspected cases of initially unexplained petechial rash in Madison area children between February and November 2007. A total of 13 cases were eventually confirmed with laboratory or clinical evidence of acute parvovirus B19 infection. Most confirmed cases had onset of rash between February and April (10 cases) with a peak in March (6 cases). Confirmed cases coincided with an abrupt increase in the number of serologically confirmed parvovirus infections among UW Health patients of all ages during the first 3 quarters of 2007 (Fig 1). There was no difference in the timing of confirmed cases and the 4 suspected cases that were not confirmed (data not shown).

Table 1 provides descriptive information about confirmed case patients. The median age of patients was 7 years (range, 3-16 years). Patients lived in a
Variety of urban, suburban, and rural locations in and around Dane County, Wisconsin. Only 2 patients, sisters 3 and 6 years old, had a known common household or school exposure. All but 1 patient received usual medical care at UW-Health. Most (9 [69%] of 13) patients were initially evaluated in a primary physician's office, and the remainder were evaluated in local emergency departments or urgent care centers.

In most cases, the presenting complaint was fever and petechial rash. Fever was reported in 11 (85%) of 13 cases, and body temperature was objectively measured in 8 of these 11 cases with maximum recorded values ranging from 38.6°C to 40.0°C. Fever was brief, ranging from 1 to 3 days, and its onset typically just preceded or coincided with discovery of the petechial rash. Associated symptoms were common and included sore throat, headache, and fatigue. Two case-patients complained that their rash was pruritic.

On physical examination, most confirmed case patients appeared well, but 4 patients were reported to be mildly or moderately ill. Petechiae were described as small (1-2 mm), flat, red or purple spots that were often present in large numbers (described, eg, as ‘100s’ or ‘too many to count’) and did not blanch. Petechiae were generalized in all cases and localized accentuated in 7 (54%) of 13 cases (Table 1).

Additional physical findings included other skin abnormalities in 5 case patients: 3 had solitary, flat, ecchymotic lesions on the chin or shin; 1 had tiny, blanching, pink papules on the back; and 1 had transient pink, blanching papules on the distal extremities, palms, and soles that preceded the generalized petechial rash. No case had palpable purpura. Six case-patients had at least 1 intra-oral finding: 3 had mucosal erythema, 2 had palatal petechiae, 1 had ulcers, and 1 had tongue papules.

Complete blood counts were available for 12 patients with confirmed cases (Table 1). Leukopenia (5000 white blood cells/mL) was found in 10 (83%) of 12 patients. Two patients had isolated neutropenia (1500 neutrophils/mL), 5 had isolated lymphopenia (1500 lymphocytes/mL), and 5 had both. Four patients had thrombocytopenia (150,000 platelets/mL) but only 1 patient had a platelet count (34,000/mL) of 100,000/mL.

TABLE 1: Selected Clinical Characteristics of Confirmed Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>1</td>
</tr>
<tr>
<td>5-9</td>
<td>8</td>
</tr>
<tr>
<td>10-14</td>
<td>3</td>
</tr>
<tr>
<td>15-19</td>
<td>1</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>Presenting complaint</td>
<td></td>
</tr>
<tr>
<td>Fever and rash</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia (elbow, shoulder)</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>13</td>
</tr>
<tr>
<td>Extremities</td>
<td>12</td>
</tr>
<tr>
<td>Head and neck</td>
<td>3</td>
</tr>
<tr>
<td>Local accentuation</td>
<td></td>
</tr>
<tr>
<td>Axillae</td>
<td>3</td>
</tr>
<tr>
<td>Groin, perineum, and/or buttocks</td>
<td>3</td>
</tr>
<tr>
<td>Distal extremities</td>
<td>2</td>
</tr>
<tr>
<td>Other physical findings</td>
<td></td>
</tr>
<tr>
<td>Cutaneous ecchymosis (chin, shin)</td>
<td>3</td>
</tr>
<tr>
<td>Intra-oral erythema, petechiae, ulcers, or papules</td>
<td>6</td>
</tr>
<tr>
<td>WBC (range)</td>
<td></td>
</tr>
<tr>
<td>5.0 (range: 0.9-14.8)</td>
<td>10</td>
</tr>
<tr>
<td>5.0-8.0</td>
<td>2</td>
</tr>
<tr>
<td>Not tested</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>150 (range: 34-144)</td>
<td>4</td>
</tr>
<tr>
<td>130-170</td>
<td>2</td>
</tr>
<tr>
<td>&gt;170</td>
<td>5</td>
</tr>
<tr>
<td>Not tested</td>
<td>1</td>
</tr>
</tbody>
</table>
Borderline or low hemoglobin concentrations (range: 10.9-11.4 g/dL) were noted in 3 patients. A reticulocyte count was measured in only 1 patient and was low (0.2%). Thorax cultures were negative for group A b-hemolytic Streptococcus (GAS) in 4 patients, and a rapid antigen test was positive for GAS in 1 (subsequently parvovirus-seroconverted) patient.

Acute parvovirus infection was laboratory confirmed in 12 of 13 cases (Table 2). Acute serum specimens were available in 11 laboratory-confirmed cases, and 3 of these cases were parvovirus IgM-negative acutely. In 2 of these IgM-negative cases, acute serum specimens were also tested for parvovirus DNA and were positive by PCR in both cases. Overall, parvovirus DNA was detectable in all 7 serologically confirmed cases tested by PCR. In the single confirmed case that was not laboratory confirmed, no serum specimen was available; however, this case was considered to be clinically confirmed because of development of classic erythema infectiosum after resolution of the petechial rash.

Six of the 13 children with confirmed cases were hospitalized. Initial diagnostic considerations for these patients included bacteremia, GAS infection, ehrlichiosis, pancytopenia, leukemia, and viral illness. Hospitalized stays were short (range: 2-3 days). All hospitalized case patients had blood cultures obtained. One case patient underwent bone marrow biopsy to evaluate neutropenia and thrombocytopenia. Two case patients developed erythema infectiosum after their petechial rash resolved; in each case, this second rash developed 2 to 3 weeks after the appearance of the first (petechial) rash.

**DISCUSSION**

In this investigation, parvovirus proved to be a common cause of petechial rash during a community outbreak of fifth disease. Relying only on passive surveillance, we were able to identify and confirm 13 cases among children and adolescents in a single health care system. This is surprising because previous English-language reports of parvovirus-associated petechial rashes described only solitary cases or small numbers of seemingly sporadic cases, although the authors of 1 report did refer (in Japanese) to an apparent cluster of 8 pediatric cases examined at a single Japanese hospital during a period of 6 months.

Parvovirus-associated petechial rashes may be more common than generally appreciated. Illnesses that are characterized by fever and petechial rash are, themselves, not rare in children and can be caused by a wide variety of viral, bacterial, and rickettsial agents. Such illnesses are not routinely evaluated for acute parvovirus infection and, typically, are attributed to unspecified (and presumed viral) agents. In the past, petechial or purpuric rashes may have been overlooked during classic investigations of large outbreaks of erythema infectiosum reported in the 1920s to 1940s, and it is notable that 2 outbreak reports from the 1950s did describe, in passing, exceptional cases of hemorrhagic rash amid hundreds of typical cases of erythema infectiosum.

Even with the advent of serologic and direct virologic methods for detecting parvovirus infection, it is still possible that cases of parvovirus-associated hemorrhagic rashes are being overlooked because previous case reports emphasized the distinctively focal nature of these rashes. Petechiae rashes in some of our cases had focal accentuation (in the distal extremities, groin, or axillae), but petechiae were widely distributed in all cases and, in this respect, more closely resembled the generalized rashes described in a few case reports.

On the basis of the clinical characteristics of our cases, it seems that parvovirus-associated petechial rash is closely linked to the viremic phase of parvovirus infection. Our case patients typically had fever, systemic symptoms, leukopenia (and occasional thrombocytopenia), and detectable parvovirus DNA in their blood, and acute-phase serum tests indicated that a specific antibody response had either not yet developed (IgM-negative) or was just developing (IgM-positive/IgG negative). Except for the petechial rash itself, these clinical characteristics closely mimic the viremic phase described in human experimental parvovirus infection, at the point (postinoculation days 9-10) when platelet and leukocyte counts reach a nadir and IgM-specific antibody begins to appear.

We speculate that the pathogenesis of parvovirus-associated petechial rash is similar to that of the papular-purpuric gloves and socks syndrome, in which parvovirus antigens can be detected directly in dermal vessel walls, as well as in cells of sweat glands and ducts and epider-
mal cells. Erythrocyte Pantigen, the receptor on the erythrocyte progenitor cell associated with the pathogenesis of the hematologic manifestations of parvovirus infection, is also present in other cell lines, including fetal cardiac myocytes and endothelial cells, and may be responsible for its skin manifestations.

The presence of a petechial rash during the acute phase of infection, when patients have viremia, could be explained by the binding of virus to Pantigen on capillary endothelial cells, thereby causing capillary disruption and extravasation of erythrocytes into dermal tissues. Endothelial cells also express the a5b1 integrin, which is a cell surface receptor necessary for infection by parvovirus B19.

The acute petechial rash and associated illness in our cases had little in common clinically with erythema infectiosum. Erythema infectiosum is believed to be a postviremic manifestation of parvovirus infection that develops 2 to 3 weeks after infection and is attributable to immune complex deposition. Typically, by the time erythema infectiosum develops in the course of acute parvovirus infection, any fever or constitutional symptoms have resolved, the peripheral white blood cell and platelet counts have normalized, and specific IgG antibodies have become detectable. Although erythema infectiosum did develop in 2 of our case patients, this occurred long after disappearance of their petechial rashes. This sequence of petechial rash followed by erythema infectiosum has been previously described and further distinguishes petechial rash in our patients from erythema infectiosum.

The principal limitation of our study is that rashes were detected by passive surveillance and, as a result, cannot be used to estimate the incidence of parvovirus-associated petechial rash. Although laboratory administrative data provide evidence that a community outbreak of parvovirus infection did occur during the study period, they provide no basis for accurately estimating the number of children infected. Moreover, although the majority of petechial rashes reported during the study period proved to be parvovirus-associated, it is possible that additional cases of petechial rash were unreported, either because they were not reported or because they were attributed to some other cause. It is also theoretically possible that the occurrence of petechial rashes in our cases reflects some variation in the strain of parvovirus that was circulating locally during the outbreak. Another limitation of our study is that diagnostic testing was not uniformly in suspect cases, and results of initial acute serum tests may have influenced whether additional (PCR or antibody) tests were ordered. Thus, the apparent sensitivity of parvovirus IgM (73%) and PCR (100%) tests in confirmed cases may be distorted by verification bias.

CONCLUSIONS

Results of our investigation during an outbreak of fever disease showed that petechial rashes may be a more common manifestation of parvovirus infection in children than suggested by previous reports of isolated cases. These rashes are typically more generalized than the focal petechial or purpuric rashes described in most reports. Associated clinical features, hematologic abnormalities, and results of serologic tests are consistent with a viremic illness that is distinct from and is occasionally even followed by erythema infectiosum.

ACKNOWLEDGMENTS

We thank the following physicians for evaluating and reporting cases: Gail Allen, James Conway, Timothy Drews, Greg Landry, Jeffrey Meade, Amy Plumb, Jeffrey Seeth, Melissa Stiles, Eric Werbasse, Robin Wright, and Kok-Peng Yu. We also thank Leanne Wheeler, UWMedical Foundation Laboratories, and David Warshauer, PhD, Wisconsin State Laboratory of Hygiene, for helping collect administrative data on parvovirus testing at UW Health and Akihiro Ikeda, PhD, for translating and reviewing Japanese medical literature.

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