Extremity Pain and Refusal to Walk in Children With Invasive Meningococcal Disease

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ABSTRACT. *Objective.* **Early recognition of invasive meningococcal disease in children may be difficult. Extremity pain and refusal to walk (extremity symptoms) are uncommonly mentioned as clinical findings in children who present with this disease. We sought to determine 1) the frequency of extremity symptoms as part of the clinical presentation in children with invasive meningococcal disease and 2) whether these symptoms help identify children with otherwise unsuspected meningococcal disease.**

Methods. **We reviewed the medical records of patients who were younger than 20 years and had invasive meningococcal disease from 1985 to 1996 at 3 pediatric referral centers. Children with extremity symptoms were identified and described. We compared clinical and laboratory findings and frequency of adverse outcomes between these children and those with invasive meningococcal disease without extremity symptoms.**

Results. **We identified 274 children with invasive meningococcal disease, 45 (16%) of whom had either history or physical examination evidence of extremity pain (31) or refusal to walk (14) as part of their clinical presentations. Five of the 45 patients had arthritis at the time of presentation. Patients with extremity symptoms at presentation were significantly older (77.9 ± 62.2 vs 44.0 ± 56.9 months), had lower temperatures (38.8 ± 1.2°C vs 39.2 ± 1.2°C), and had higher band counts (28.2 ± 15.2% vs 18.1 ± 12.4%) than did patients without extremity symptoms. There were no significant differences, however, between groups with regard to rash, white blood cell counts, coagulation parameters, prevalence of meningitis, or adverse outcomes. Seventy-three (27%) of the 274 patients had unsuspected disease, and 5 (7%) of these had extremity symptoms at the time of diagnosis.**

Conclusions. **Sixteen percent of children with invasive meningococcal disease have extremity symptoms at the time of diagnosis. These symptoms may help to identify some patients with otherwise unsuspected invasive meningococcal disease.** *Pediatrics* **2002;110(1). URL: http://www.pediatrics.org/cgi/content/full/110/1/e3;** ***meningococcal infections, fever, bacteremia, myalgia, limp.***

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ABREVIATIONS. CSF, cerebrospinal fluid; WBC, white blood cell; PT, prothrombin time; PTT, partial thromboplastin time; OR, odds ratio; CI, confidence interval; DIC, disseminated intravascular coagulation.

The clinical manifestations of invasive meningococcal disease in children typically consist of fever with toxic clinical appearance, irritability, lethargy, nuchal rigidity, hypotension, and petechial/purpuric rash.[1–6] Some children with invasive meningococcal disease, however, present in a more subtle manner with fever without clinical toxicity and other nonspecific symptoms, such as cough, rhinorrhea, vomiting, and headache, resembling an upper respiratory tract infection or other viral illness.[5–7] Although early recognition and treatment of meningococcal disease decreases complications,[7] neither the physical examination nor the hematologic evaluation reliably enables health care providers to differentiate these children from those with other, less serious illnesses.[5] The identification of clinical findings that might further assist the clinician in making an early diagnosis of meningococcal infection could potentially improve outcomes from this disease.

Muscle and joint pain, particularly associated with arthritis and gait disturbance, are sporadically but not uniformly mentioned in review articles and textbooks as features of meningococcal disease.[1,4,6] In the course of reviewing charts of children with invasive meningococcal disease in previous investigations,[5,7–9] we noted that extremity pain and refusal to walk were not uncommon clinical findings at the time of presentation. We considered whether these findings, in association with other nonspecific symptoms, might prompt clinicians to consider the diagnosis of invasive meningococcal disease in the evaluation of a febrile child.

The purpose of the study was to 1) determine the frequency of extremity pain and/or refusal to walk as part of the clinical presentations in children with invasive meningococcal disease and 2) determine whether extremity pain or refusal to walk help to identify children with otherwise unsuspected meningococcal disease. We hypothesized that extremity pain and refusal to walk are not uncommon presenting clinical findings in children with invasive meningococcal disease and that these findings may help to identify children with unsuspected meningococcal disease.

METHODS

Patient Population

We reviewed the medical records of all patients who had meningococcal bacteremia and/or meningitis, were younger than 20 years, and were evaluated at 3 urban, geographically distinct pediatric referral centers from January 1, 1985, to December 31, 1996. Approval was obtained from the investigational review board at each institution. We identified these patients by reviewing admission diagnosis log books, microbiology log books, and/or *International Classification of Diseases, Ninth Revision*[10] discharge codes from medical records at each institution. The medical records were reviewed in a structured format, using a standardized data collection sheet. Subsets of this population have been studied and reported previously.[3,5,7–9,11]

Definitions

Invasive meningococcal disease was defined by a positive blood or cerebrospinal fluid (CSF) culture and/or positive latex agglutination tests of the blood or CSF for *Neisseria meningitidis*.

Meningitis was defined as the isolation of *N meningitidis* in the CSF culture or a CSF white blood cell (WBC) count ≥10 cells/mm^3 in association with a positive blood culture or a positive CSF latex agglutination study. When the lumbar puncture had been traumatic (ie, CSF red blood cell count >10 000 cells/ mm^3), the patient was classified as having an unknown meningitis status.

Extremity pain was defined as discomfort of any upper or lower extremity, including muscle pain and/or joint pain. Refusal to walk was defined as reluctance to walk or stand in patients in whom there was no evidence that lethargy or obtundation were the causes. In addition, patients who refused to walk because of pain, including extremity pain and back pain, were included in this category. Extremity symptoms were defined as a history or physical examination demonstrating extremity pain or refusal to walk.

Arthritis was defined as joint pain that was associated with either the presence of swelling, erythema, and/or fluctuance or an arthrocentesis that was positive for *N meningitidis* and/or a WBC count of >50 000 cells/mm^3 in the joint fluid. Coagulopathy was defined as any or all of the following: prothrombin time (PT) ≥20 seconds or partial thromboplastin time (PTT) ≥60 seconds or fibrinogen <250 mg/dL. Adverse outcomes were considered to be death, limb amputation, or amputation of all 5 digits on 1 limb.

Children were considered to have unsuspected meningococcal disease when they were evaluated and discharged home as outpatients and had *N meningitidis* isolated from blood and/or CSF cultures obtained during these outpatient evaluations. Children were considered to have possible unsuspected meningococcal disease when they had been evaluated for febrile illnesses as outpatients in the 48 hours before hospitalization but did not have blood or CSF cultures obtained at these outpatient evaluations.

Data Collection

Data were collected from the medical records of patients with invasive meningococcal disease at each institution using a standardized data collection sheet. Patients with signs or symptoms of extremity pain or refusal to walk by history or on physical examination were identified. We considered extremity pain or refusal to walk to be present only when these findings were recorded by a physician at the time of the emergency department or initial inpatient history and physical examination and were related to the current acute illness. In addition, we collected the following data: demographic information, clinical and laboratory findings documented at the presenting visits (including the outpatient visits during which diagnostic cultures were obtained), complications, and adverse outcomes.

Statistical Analysis

We compared patients with extremity symptoms with patients without these symptoms with regard to baseline clinical and laboratory findings, presence of meningitis, and adverse outcomes. Student *t* test was used to analyze continuous variables and Fisher exact test was used to compare categorical variables. All tests were performed based on 2-tailed alternatives. $P \leq .05$ was considered to be significant and values from .05 to .10 to represent a trend. All statistical analyses were performed using Stata statistical software, version 6.0 (Stata Corp, College Station, TX).

RESULTS

A total of 274 patients with invasive meningococcal disease were identified. Demographic information (age and gender), clinical characteristics (temperature, rash), and laboratory characteristics (WBC counts, band counts, CSF findings) were described previously in large subgroups of this study population.[3,5,7–9,11] Two percent of the patients had arthritis at presentation. Thirty-six (13%) of the 274 patients had adverse outcomes, and 26 (72%) of these 36 died. Seventy-three (27%) of the patients had unsuspected meningococcal disease or possible unsuspected meningococcal disease. Five (7%) of these unsuspected patients had extremity symptoms identified at an outpatient visit or on their initial inpatient history and physical examination.

Of the 274 patients, 45 (16%) had extremity symptoms at the time of presentation. Twenty (44%) of these patients had only a history of these symptoms documented, 4 (9%) had these symptoms documented at the time of the physical examination, and 21 (47%) had these symptoms documented by both history and physical examination. Table 1 details the spectrum of extremity symptoms.

All 5 patients with arthritis at presentation had extremity (joint) pain at the time of presentation. Two of these patients also refused to walk. Of the other 40 patients with nonarthritic extremity symptoms at the time of presentation, 5 developed signs of arthritis while in the hospital. Only 1 of these patients had joint pain at the time of presentation. Twelve of the remaining 35 patients with nonarthritic extremity symptoms had joint pain with or without other associated extremity symptoms but did not have arthritis at presentation or develop arthritis in the hospital. In addition, 5 (2%) of the 229 patients without extremity symptoms at presentation developed arthritis while they were in the hospital. Nine of the 15 total patients with arthritis at the time of presentation or during the hospitalization had

TABLE 1. Specific Clinical Findings in Patients With Extremity Pain* and Refusal to Walk

Symptom or Sign	Number of Patients
Extremity pain alone*	31
Extremity and/or muscle pain	12
Muscle and joint pain	5
Joint pain alone and/or swelling	8
Extremity or joint pain and back pain	2
Decreased movement of an extremity	4
Refusal to walk alone	3
Refusal to walk and extremity*/back pain	11
Extremity or muscle pain	3
Muscle and joint pain	1
Joint pain alone and/or swelling	3
Extremity and/or back pain	3
Decreased movement of an extremity	1
*Location of extremity pain (40 patients)	
Upper extremity	4
Upper and lower extremity	19
Lower extremity	17

joint aspirations performed, and all were culture negative.

Demographic information and clinical and laboratory characteristics of patients with extremity symptoms are compared with those without symptoms in Table 2. Patients with extremity symptoms were older and had higher band counts than patients without such symptoms. The temperatures of those with extremity symptoms were lower than in those without, and petechial/purpuric rashes were more likely to be present.

There was a trend toward lower PT and PTT values in children with versus those without extremity symptoms, suggesting less coagulopathy in the extremity symptom group compared with those without extremity symptoms. Three of the 35 patients (9%) who had extremity symptoms and had coagulation parameters measured had a coagulopathy compared with 33 (26%) of the 127 without symptoms ($P = .04$). There were no significant differences, however, in mean platelet counts or serum fibrinogen concentrations between the 2 groups.

Thirty of the 40 patients (75%) who had extremity pain or refused to walk and had lumbar punctures performed had meningitis compared with 163 (82%) of the 199 patients who did not have extremity symptoms and had lumbar punctures performed (odds ratio [OR]: 0.66; 95% confidence interval [CI]: 0.30–1.45; $P = .38$). The diagnosis of meningococcal meningitis was made in 11 of these patients by means of positive CSF latex agglutination tests (including 2 patients with extremity symptoms). All had a CSF WBC count ≥500 cells/mm^3 and had other features of meningococcal disease, such as petechial/purpuric rash in 9 of these patients, including the 2 patients with extremity symptoms.

Four (9%) of the 45 patients with extremity symptoms had adverse outcomes compared with 32 (14%) of the 229 patients without symptoms. (OR: 0.60; 95% CI: 0.21–1.72; $P = .47$). Of these, 3 patients with extremity symptoms (7%) died compared with 23 (10%) without symptoms (OR: 0.63; 95% CI: 0.20–2.10; $P = .59$).

DISCUSSION

In this study, we found that 45 (16%) of 274 children with invasive meningococcal disease had extremity symptoms as part of their presenting histories and/or physical examinations. Of these 45 children, 5 (11%) had arthritis at the time of presentation and 5 others went on to develop arthritis in the hospital. There was no difference in the prevalence of meningitis between those who had extremity symptoms and those who did not have these symptoms. In addition, we found that 5 (7%) of 73 children with unsuspected meningococcal disease or possible unsuspected meningococcal disease had extremity symptoms at an outpatient visit or on their initial inpatient histories and physical examinations.

We are aware of only 1 previous study[12] of children with meningococcemia that mentions extremity symptoms, other than arthritis, as a clinical manifestation of this disease. In that study 16 (11%) of 152 patients had "walking problems" listed in a table, but there was no discussion of this finding as a significant feature and it is not clear whether any of these patients had arthritis. In addition, at least 1 textbook[4] describes extremity pain other than arthritis as a presenting complaint based on case reports of patients with meningococcemia and extremity pain.[13,14] A recent review article briefly mentioned arthritis as a clinical manifestation of meningococcal disease but did not associate other extremity symptoms with this disease.[15]

Localized muscle pain, especially of the calf muscles, and joint pain were frequent complaints in a case series of 26 World War II troops with meningococcal infection.[13] Another case series described 4 febrile adults with bacteremia, 1 of whom had meningococcemia, who presented with severe anterior thigh pain/tenderness.[16] One of these patients was unable to walk. On the basis of their cases, the au-

TABLE 2. Comparisons of Clinical and Laboratory Characteristics Between Patients With and Without Extremity Symptoms

Baseline Characteristic	Patients With Extremity Symptoms ($n = 45$)	Patients Without Extremity Symptoms ($n = 229$)	Difference Between Means or Percentages (95% CI)	P Value
Age (mean; mo)	77.9 ± 62.2	44.0 ± 56.9	33.9 (15.4 to 52.5)	<.001
Male (n; %)	32 (71)	137 (60)	11% (−3 to 26%)	.18
Temp (°C)*	38.8 ± 1.2	39.2 ± 1.2	.40 (.01 to .78)	.04
Rash (n; %)†	35 (78)	135 (64)	14% (0.3 to 28%)	.08
WBC (×10^3/mm^3)‡	15.3 ± 8.4	14.8 ± 9.2	.5 (−2.5 to 3.4)	.74
Bands (%)§	28.2 ± 15.2	18.1 ± 12.4	10.1 (5.6 to 14.5)	<.001
Platelets (×10^3/mm^3)‖	240 ± 116	268 ± 143	28 (−18 to 74)	.23
PT (seconds)¶	15.0 ± 2.7	16.6 ± 9.6	1.6 (−0.3 to 3.6)	.09
PTT (seconds)#	38.4 ± 16.5	45.1 ± 24.9	6.7 (−0.4 to 13.7)	.06
Fibrinogen (mg/dL)**	469 ± 170	426 ± 272	43 (−48 to 136)	.35
Adverse Outcome (n; %)††	4 (9)	32 (14)	5% (−15 to 4%)	.47

* Measured in 270 of 274 patients (all patients with symptoms).
† Recorded in 257 of 274 patients (all patients with symptoms).
‡ Measured in 271 of 274 patients (44 of 45 patients with symptoms).
§ Measured in 243 of 274 patients (40 of 45 patients with symptoms).
‖ Measured in 246 of 274 patients (43 of 45 patients with symptoms).
¶ Measured in 155 of 274 patients (32 of 45 patients with symptoms).
# Measured in 162 of 274 patients (36 of 45 patients with symptoms).
** Measured in 111 of 274 patients (23 of 45 patients with symptoms).
†† Adverse outcome defined as death, limb amputation, or amputation of all 5 digits on 1 limb.

thors encouraged physicians to include bacteremia from organisms such as *N meningitidis* and *Staphylococcus aureus* as part of the differential diagnosis in febrile patients with anterior thigh pain. The relationship of limp to meningitis was also discussed in a report of 2 children who presented with fever, musculoskeletal pain, and limp and had acute meningococcal disease with meningitis.[17] Of note, in both cases, the children reported extremity pain on history, but, as with some patients in our study, there were few or no objective findings on physical examination.

Complaints of limp or gait disturbances from extremity pain or other causes are common in children.[18,19] Refusal to walk is a much less common complaint and usually suggests a more serious illness than limp alone.[20] There are many causes of these complaints described in the literature, including viral or postviral (reactive) arthritis/arthralgia and bacterial myositis[18–20]; however, neither meningococcemia nor bacteremia/sepsis is listed as a cause of limp or refusal to walk in pediatric reviews of these topics. Myalgia may occur in association with fever and viral illness.[21,22] However, as an example, the myalgia associated with influenza is an uncommon clinical manifestation in children younger than 5 years,[21] an age group in which meningococcemia is most prevalent.[1,2,4–9]

The cause of extremity pain and refusal to walk in children with meningococcemia likely is multifactorial. Joint inflammation from bacterial seeding or from immune complex deposition,[23,24] inflammatory mediators causing muscle pain,[22,25] and thrombosis from disseminated intravascular coagulation (DIC) causing bony infarcts all may play a role.[26,27]

Arthritis is a well-recognized clinical finding in children with meningococcemia and occurs in approximately 5% of those infected during the acute course of this disease.[23] Arthritis usually occurs from direct bacterial invasion of the synovium (septic arthritis) or more frequently as a hypersensitivity reaction several days into the acute course with immune complexes present in the synovial fluid.[23,24] Of the 274 patients in our study, 15 (5.5%) either had arthritis at presentation or went on to develop arthritis in the hospital as part of their clinical courses.

In addition to the above patients with arthritis, there were another 12 patients in the extremity symptom group who had joint pain but did not have arthritis at presentation or develop arthritis in the hospital. The joint pain experienced by these patients was possibly attributable to immune complex deposition or, perhaps, from the seeding of meningococci in the synovium or extra-articular connective tissue that causes pain without the typical clinical manifestation of joint inflammation.[4,28]

Numerous studies have demonstrated increased serum concentrations of inflammatory mediators in patients with meningococcemia,[29,30] and these may play a role in the extremity pain experienced in patients with meningococcemia. It is known that interleukin-1 increases proteolysis in muscle without increasing muscle protein synthesis.[22] Interleukin-1 also stimulates muscle synthesis of prostaglandin E_2 that may result in muscle protein breakdown and sensitizes peripheral pain receptors and causes hyperalgia.[25]

A vascular insult from DIC that commonly occurs in invasive meningococcal disease[1,3,11] is another potential cause of extremity pain. The deposition of fibrin and thrombus formation associated with DIC may lead to limb/digit loss.[11] In some cases, however, bone infarction from occlusion of small vessels without limb loss occurs in patients with meningococcemia and DIC.[26,27]

The main finding of our study is that extremity pain and/or refusal to walk either by history or physical examination are not uncommon clinical findings in patients with invasive meningococcal disease. Although not as frequent as fever with toxic appearance, rash, or neck stiffness that are commonly described in association with invasive meningococcal disease, extremity pain and refusal to walk are as frequent as other often described presenting signs and symptoms associated with this disease, such as seizures and irritability.[2,4,6]

We also found that 5 of 73 patients with unsuspected or possible unsuspected meningococcal disease had symptoms of extremity pain or refusal to walk at the time of diagnosis. The presence of extremity pain or refusal to walk in patients with a febrile illness should raise the possibility of meningococcemia, especially in selected clinical situations with higher probability of meningococcal disease such as in patients with known contacts with cases of meningococcal disease,[4,31] outbreaks of meningococcal disease,[31,32] or in patients with fever associated with petechial rashes.[33–35] Additional groups of patients who are at risk for meningococcal disease include college freshmen, particularly those who live in dormitories,[36] and adolescents or young adults who visit local bars or nightclubs.[37,38] When considering meningococcal disease, clinical evaluations should include these historical items.

There are several potential limitations to this study. As this was a retrospective study, it is likely that some patients and their families were not asked about the presence of extremity pain and that some physical examination findings may not have been documented. The reported frequencies of extremity symptoms, therefore, likely underestimate the true frequency of these symptoms in children with invasive meningococcal disease. In addition, if children were too young to describe their symptoms, then extremity findings likewise may have gone undetected. It is also possible that lethargy, obtundation, or ataxia[39] may have contributed to the refusal to walk in some cases, although we attempted to exclude these patients from the group with extremity symptoms. Finally, in this case series, we did not compare the patients with extremity symptoms with a "viral" control group. Age-matched control children with febrile illnesses frequently do not have blood cultures and other laboratory tests obtained and often do not have documentation of their follow-up evaluations. Therefore, identifying a true "viral" control group would be difficult and potentially misleading in a retrospective review.

CONCLUSION

Approximately one sixth of children with invasive meningococcal disease have extremity pain or refusal to walk as part of the symptom complex of this disease at the time of presentation. These symptoms may help to identify some patients with otherwise unsuspected invasive meningococcal disease. We suggest that 1) although extremity pain and refusal to walk are nonspecific clinical findings in febrile children, these signs and symptoms should raise the possibility of invasive meningococcal disease; and 2) febrile children with extremity pain or refusal to walk in selected clinical situations with a higher previous probability of meningococcal disease should be carefully evaluated for the possibility of invasive meningococcal disease.

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