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Abstract

We carried out a case–control study in children with acute hematogenous osteomyelitis (AHO) with and without suppurative complications discharged from our institution over an 11-year period to test the hypothesis that abscess formation was associated with a delayed presentation to care. Of 102 children with AHO, 54 abscesses were documented in 46 patients (25 bone, 29 muscle). A delay in presentation was not associated with abscess formation (6.5 vs. 5.0 days, $P = 0.26$). Overall, 78% of all bone abscesses were visible on initial MRI. Consistent use of MRI at presentation may identify children with suppurative complications of AHO.

Keywords

abscess; osteomyelitis; pyomyositis

Introduction

Acute hematogenous osteomyelitis (AHO) is one of the most commonly diagnosed infections in healthy children requiring prolonged antimicrobial therapy. In high-income countries such as the USA, approximately eight in 100 000 children will develop AHO during their lifetime, with most cases occurring in children younger than 12 years of age [1–3]. *Staphylococcus aureus* is the most frequent pathogen isolated in pediatric AHO, although a variety of pathogens may be encountered [1,4–11]. Although full recovery is common, abscesses of bone and contiguous musculature may complicate AHO and have been associated with infection with methicillin-resistant *Staphylococcus aureus* (MRSA) [11–15]. Although the majority of children with AHO are successfully treated with antimicrobial

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agents alone, surgery may be needed for drainage of bone or muscle abscesses [1,16–19]. MRI is the optimal modality for visualizing the suppurative complications of AHO, but is often ordered early in the clinical course and it is unclear when suppurative complications are most likely to appear. Children with abscess formation may also experience complicated hospitalizations, marked by multiple surgeries, serial imaging, central venous catheter placement for prolonged courses of parenteral antimicrobial therapy, and prolonged hospital stays [14].

Despite the frequency with which AHO affects children, little research has been carried out on the risk factors and clinical course associated with AHO complicated by bone and muscular abscesses. Arnold *et al.* [14] reported an association with complicated recoveries in children with acute MRSA osteoarticular infections. In this series, children with AHO and subperiosteal abscesses were nearly twice as likely to be infected with MRSA compared with methicillin-susceptible *Staphylococcus aureus* (MSSA) (71.0 vs. 38.0%, $P = 0.02$). However, this study did not assess the effect that a delay in presentation to care may have on abscess formation, nor did it provide any detailed information on those children with suppurative complications. Ratnayake *et al.* [20] described a population of 75 children with AHO, 59% of whom developed suppurative complications of the bone or soft tissue. However, neither the effect of the timing of presentation to care nor the clinical characteristics of the patients with abscesses were addressed by the study.

As the only tertiary care facility in our state, our institution evaluates almost all of our state's pediatric AHO. Over the last several years, we believed that a large percentage of our children with AHO developed suppurative complications of either the bone or muscle. We hypothesized that these complications were associated with a delayed presentation to care, likely as a result of the rural nature of our state. Given the lack of any published study dedicated to this question, as well as the unique opportunity to explore this, given the rural nature of our state, we completed a case–control study of children treated at our hospital with AHO with and without suppurative complications to test this hypothesis. As a secondary goal, we also sought to provide the first detailed description in the literature of the clinical course associated with suppurative complications of AHO.

Materials and methods

Otherwise healthy children (1 month–18 years) discharged from the University of New Mexico Health Sciences Center between 1 March 2003 and 1 March 2014 were retrospectively screened for a discharge diagnosis of AHO utilizing the following ICD-9 codes: acute osteomyelitis (730.00–730.09), chronic osteomyelitis (730.10–730.19), pyogenic arthritis (711.00–711.09), and unspecified osteomyelitis (730.20–730.29). Although only cases of AHO were included, codes for chronic osteomyelitis and pyogenic arthritis were included to screen for any misclassification of discharge codes that may have occurred and/or any coexistent AHO. Imaging of each case was reviewed and abnormalities of the affected bone consistent with AHO were required for inclusion at some point during the patients' clinical course. In addition, a clinical history compatible with AHO was required after review of the medical record by Pediatric Infectious Disease Faculty (W.D.). Patients with AHO and associated suppurative complications of the bone or muscle were

included as cases, whereas patients with AHO without such complications were included as controls. Patients with chronic osteomyelitis, osteomyelitis following fractures, orthopedic-implant associated osteomyelitis, or osteomyelitis occurring in the same bone after orthopedic surgery were excluded. Hospital-acquired osteomyelitis cases were also excluded as our study focused on community-acquired disease. In addition, patients with vertebral osteomyelitis and patients under 1 month of age were excluded as it is the standard of care in our institution to treat these patients with prolonged courses of parenteral therapy, which could confound assessments of disease severity.

Intraoperative confirmation was required for the diagnosis of a bone abscess as several conditions may present with similar radiographic appearances (e.g. hematoma). Muscular abscesses required MRI documentation only. Superficial abscesses (e.g. cutaneous involvement only) were excluded. After verification of disease status, study data were collected and managed using REDCap electronic data capture tools hosted at our institution [21]. Data entry was crosschecked by two investigators to verify accuracy (J.J. and W.D.). This project was approved (approval #14–099) by the Human Research Protections Office at the University of New Mexico.

Statistical analysis

This case–control study was descriptive in nature, with all patients who fulfilled inclusion criteria included during a 1-year interval. Summary statistics calculated included medians and quartiles for continuous variables, and frequencies and percentages for categorical variables. Post-hoc comparisons were performed using Wilcoxon-rank sum tests to compare continuous variables between cases and controls, whereas χ^2-tests were used for categorical variables. The odds ratio, the corresponding 95% exact confidence interval, and two-sided Fisher's exact test were calculated to compare the long-term complication rates in patients with and without abscesses. Bonferroni corrections were applied to the type I error rate for groups of tests performed together and the significance level for assessing P-values is provided in the footnotes for each table. All analyses were carried out in SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Demographic data

Of 427 patients identified in our initial search, 102 patients fulfilled the inclusion criteria. A total of 163 patients were excluded due to an age outside the study inclusion criteria, admission date beyond the study timeline, or use of an ICD-9 code not specified by the study, whereas 162 patients were excluded because of lack of evidence of AHO. Table 1 outlines the demographic features of our cohort. In all, 27 girls and 75 boys were included, mean age 7.5 years. Overall, 48% of the patients were Latino, 26% were White, 15% were Native American, 11% were of unknown ethnicity, and 1% was African American.

Clinical presentation

Overall, 25 (25%) patients with AHO in our cohort developed a bone abscess, 29 (28%) patients developed a muscular abscess, and eight patients had both bone and muscular

abscesses (Table 1). Hence, taking into account the eight patients with both a bone and a muscular abscess, 46 (45%) individual patients developed at least one abscess. The most common bones affected by abscess formation were the tibia and the fibula (44%), followed by the femur (28%). Of the 25 bone abscesses identified, nine were described intraoperatively as an intraosseous abscess and 16 as a subperiosteal abscess. Muscle abscesses were contiguous with the associated osteomyelitis in 64% of cases. Twenty-one (72%) of 29 muscle abscesses required operative drainage; the rest were treated medically.

It is noteworthy that a delayed presentation to care was not associated with suppurative complications, as the median time to presentation after symptom onset was similar between those children with and without suppurative complications (6.5 vs. 5.0 days, respectively, $P = 0.26$). However, children with suppurative complications presented with significantly higher C-reactive protein (CRP) values and erythrocyte sedimentation rates (ESRs) on admission than those without such complications (CRP = 13.5 vs. 5.1 mg/dl, $P < 0.0001$ and ESR = 77.0 vs. 44.0 mm/h, $P = 0.0005$, respectively).

Pathogens involved

Three different pathogens were isolated from 25 bone abscesses: MSSA (60%), MRSA (32%), *Streptococcus pyogenes* (4%), and *Salmonella montevido* (4%) (Table 2). MRSA was involved in 45% of 29 muscular abscesses, with MSSA involved in 35% (no pathogen was isolated from 21% of muscular abscesses). Overall, *S. aureus* was isolated from 83% of all abscess cultures (46% MSSA, 37% MRSA) and 95% of all cultures with growth. A broader variety of pathogens was associated with AHO without suppurative complications, with seven different organisms isolated. Among patients without suppurative complications, however, *S. aureus* was still the pre-dominant organism, with 60% of cases with growth on culture attributable to *S. aureus* (33% MRSA, 27% MSSA). *S. aureus* was significantly more likely than other organisms to be associated with suppurative complications than other pathogens ($P = 0.0003$), although no significant difference in the risk of abscess formation was noted between MRSA and MSSA ($P = 0.45$).

Timing of diagnosis

The majority of suppurative complications were diagnosed early in the hospital course. Bone abscesses were diagnosed on average by hospital day 4 (range: 1–45 days, median: 1 day). Overall, 56% of all bone abscesses were diagnosed on the day of admission. Muscular abscesses were diagnosed on average by hospital day 2 (range: 1–6 days, median: 1 day), with 52% of muscular abscesses diagnosed on the day of admission. Bone abscesses were visible on the initial MRI obtained during the hospital stay 78% of the time; the rest were detected on subsequent imaging. Among all patients in our cohort, 81 (79%) patients had at least one MRI.

Short-term outcomes

Patients with suppurative complications underwent twice as many MRI studies of the affected area (2 vs. 1, $P = 0.0008$), required a longer duration of total antimicrobial therapy (median: 56 vs. 45 days, $P = 0.0004$), a longer duration of parenteral therapy (median: 29 vs. 9 days, $P = 0.0002$), longer hospital stays (median: 13 vs. 8 days, $P < 0.0001$), and had a

longer duration of fever (median: 5 vs. 1 day, $P < 0.0001$) (Table 3). Children with abscess formation also required significantly more surgical interventions ($P < 0.0001$, Table 3). Within our study cohort, the maximum median CRP was higher for those children with suppurative complications versus those without (18.0 vs. 6.1 mg/dl, respectively, $P = 0.0002$), whereas the maximum ESR (median) was 88 mm/h compared with 50 mm/h ($P < 0.0001$, respectively). Five patients with bone abscesses were readmitted, with one patient requiring a total of three readmissions.

Late-onset complications

Thirty of the 46 patients with abscesses had at least a 3-month follow-up visit. Eight (27%) of these patients experienced complications (Table 4). Among the 56 patients with no abscesses noted, 27 had at least 3 months of follow-up, three (11%) of whom experienced complications (Table 4). The late-onset complication rate between those with and without noted abscesses was not statistically different (odds ratio = 2.9; 95% confidence interval =0.6–18.8).

Discussion

Suppurative complications of AHO were not associated with a delayed presentation to care in our study cohort. However, such children experienced more severe illnesses compared with children without abscess formation. To our knowledge, this is the first study to assess the impact that a delayed presentation to care may have on abscess formation in AHO and the first to provide a detailed description of the presentation and clinical course of such patients. The majority of abscesses were diagnosed early in the hospital stay (over half at admission, with an overall median time to diagnosis of 1 hospital day). Not surprisingly, children with abscesses in our cohort did present with significantly higher CRP and ESR values at admission than those without such complications. CRP levels are elevated during the acute phase of inflammation, with a half-life of 19 hours, making it a valuable tool for the assessment of disease severity and the early identification of at-risk patients [22]. Mirroring our findings, Arnold *et al.* [23] also found CRP levels to be the highest in children with complicated outcomes, which included one child with subperiosteal abscess formation. In addition, the routine use of MRI at presentation would likely identify the majority of children with suppurative complications as nearly 80% of all abscesses in our patient population were identified on the initial MRI obtained during hospitalization. Given this, as well as the frequency with which suppurative complications was observed in our cohort (45% of all patients), universal use of MRI at presentation in all children with suspected AHO may be justified. Given that these complications required significantly more surgical interventions, early diagnosis would likely affect management and clinical outcomes. Interestingly, the frequency of late-onset complications was nearly three times more common among those with abscess formation; however, this was not statistically significant and the low number of patients with such complications in our cohort as well as the lack of complete follow-up on all patients prevent us from drawing definitive conclusions. To our knowledge, ours is the first study to report on late-onset outcomes of patients with suppurative complications of AHO.

On comparing muscular and bone abscess patients, both groups showed a similar frequency of *S. aureus* infection. However, children with bone abscesses had significantly more severe disease courses, requiring a longer duration of therapy, longer hospitalizations, a longer time to defervescence, higher initial and maximum CRP values, and higher rates of readmission and relapse.

Contrary to our initial hypothesis, a delayed presentation to care was not related to abscess formation. Our study also failed to find an association between MRSA and suppurative complications compared with MSSA. This is in contrast to the findings of Arnold *et al.* [14] who described a significant association between MRSA osteomyelitis and the development of subperiosteal abscess formation. This discrepancy may in part be related to host-pathogen genetic differences, a theory supported by the lack of an association in our cohort between abscess formation and any modifiable risk factors such as a delayed presentation to care or a delayed diagnosis of the suppurative complication in the hospital after admission. *S. aureus* virulence factors predisposing to suppurative complications may also be unrelated to antimicrobial resistance (e.g. intrinsic to either MSSA or MRSA). The frequency with which MRSA or MSSA clones with particular virulence factors are present in a given population likely varies as well [24]. Previous work has reported unique transcriptomic profiles present in MRSA isolates associated with more complicated disease [15,25,26]. Loughman *et al.* [27] reported higher levels of gene expression of surface-associated protein A from MRSA isolates obtained from children with invasive disease compared with those with superficial/cutaneous infections. Interestingly, long-term complications in our cohort were encountered in patients with or without abscesses (and with either muscle or bone abscesses), suggesting that such complications may, at times, arise as a result of the virulence of the infecting organism and not secondary to anatomic or structural damage to the bone incurred from the abscess itself. Analysis of potential genetic determinants of suppurative complications (both host and pathogen) may help explain a potential genetic predisposition to abscess formation.

Our study has several limitations. The retrospective nature of the data collection predisposes to observational biases as we relied on electronic medical records of variable quality. Not every patient underwent imaging with an MRI in our cohort, which may have led to an ascertainment bias and nondifferential misclassification of cases, which would likely underestimate the true incidence of suppurative complications. In addition, given the 11-year period over which our data were collected, provider turnover may have differentially affected management approaches over time. Follow-up for late-onset complications was also unavailable for many patients (only 56% received a documented 3-month follow-up), which may lead to an underestimation of these complications. Finally, although it is not surprising that patients with abscess formation experienced worse outcomes acutely, we believe that our data help quantify these outcomes for the first time and provide prognostic guidance for providers and families. In addition, the data also characterize the impact and frequency of late-onset complications, and highlight the utility of early CRP and MRI assessment in detecting abscess formation, none of which are well described in the literature.

Conclusion

Our study showed a high incidence of abscess formation in children with AHO that was not attributable to a delayed presentation to care. These children experienced a more severe clinical illness than those without abscess formation. Early risk stratification with the use of universal MRI imaging for children with suspected AHO at admission may lead to early identification of suppurative complications.

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Table 1

Presenting characteristics of 102 pediatric patients with acute osteomyelitis with and without abscess formation

Variables		Bone abscess (n = 25)	Muscle abscess (n = 29)	Any abscess (n = 46)	No abscess (n = 56)	P-value for any vs. no abscess
Demographic characteristics[a]	Sex [n (%)]					
	Male	19 (76)	23 (79)	36 (78)	39 (69)	0.33[2]
	Female	6 (24)	6 (21)	10 (22)	17 (30)	
	Age [median (Q1, Q3)] (years)	9.0 (3.0, 11.2)	9.8 (5.8, 12.5)	9.5 (4.4, 12.0)	6.0 (2.0, 10.0)	0.02[1]
	Ethnicity [n (%)]					
	White	10 (40)	11 (38)	15 (33)	11 (20)	0.29[2]
	Hispanic	10 (40)	13 (45)	21 (46)	28 (50)	
	Native American	4 (16)	3 (10)	7 (15)	8 (14)	
	Other	1 (4)	2 (7)	3 (7)	9 (16)	
Baseline clinical characteristics[b]	Time to Presentation [median (Q1, Q3)] (days)	7.0 (5.0, 11.0)	7.0 (4.0, 13.0)	6.5 (3.5, 12.0)	5.0 (2.0, 14.0)	0.26[1]
	Admission WBC count [median (Q1, Q3)] (cells/ml)	11.4 (9.4, 14.9)	13.7 (10.0, 18.3)	12.0 (9.5, 17.4)	12.2 (8.8, 14.9)	0.72[1]
	Admission CRP [median (Q1, Q3)] (mg/dl)	17.3 (11.5, 24.2)	12.3 (5.0, 24.1)	13.5 (6.6, 25.3)	5.1 (1.9, 9.4)	< 0.0001[1]
	Admission ESR (mm/h), Median (Q1, Q3)	81.5 (56.0, 105.0)	84.0 (39.5, 101.5)	77.0 (38.0, 101.0)	44.0 (18.0, 60.0)	0.0005[1]
	Location of osteomyelitis [n (%)]					
	Femur	7 (28)	6 (21)	10 (22)	12 (21)	0.97[2]
	Tibia/fibula	11 (44)	7 (24)	15 (33)	17 (30)	0.81[2]
	Pelvis	2 (8)	6 (21)	7 (15)	7 (12)	0.69[2]
	Ankle/foot	5 (20)	5 (17)	8 (17)	9 (16)	0.86[2]
	Humerus	3 (12)	3 (10)	6 (13)	2 (4)	0.08[2]
	Radius/ulna	0 (0)	1 (3)	1 (2)	1 (2)	1.00[3]
	Other	4 (16)	6 (21)	8 (17)	11 (20)	0.77[2]

Variables	Bone abscess (*n* = 25)	Muscle abscess (*n* = 29)	Any abscess (*n* = 46)	No abscess (*n* = 56)	*P*-value for any vs. no abscess
Multifocal osteomyelitis	6 (24)	11 (38)	14 (30)	6 (11)	0.01[2]

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

[a] Compare *P*-values in this subset to Bonferroni-corrected type I error rate = 0.017.

[b] Compare *P*-values in this subset to Bonferroni-corrected type I error rate = 0.0042.

[1] *P*-value obtained from the Wilcoxon-rank sum test.

[2] *P*-value obtained from the χ^2-test.

[3] *P*-value obtained from the Fisher exact test.

Table 2

Association of pathogen and abscess formation

Pathogen	Bone abscess (*n* = 25) [*n* (%)]	Muscle abscess (*n* = 29) [*n* (%)]	Any abscess (*n* = 46) [*n* (%)]	No abscess (*n* = 56) [*n* (%)]
MRSA*	8 (32)	13 (45)	17 (37)	10 (18)
MSSA*	15 (60)	10 (34)	21 (46)	8 (14)
Streptococcus pyogenes	1 (4)	0 (0)	1 (2)	4 (7)
Streptococcus pneumoniae	0 (0)	0 (0)	0 (0)	1 (2)
Salmonella montevido	1 (4)	0 (0)	1 (2)	0 (0)
Kingella kingae	0 (0)	0 (0)	0 (0)	1 (2)
Haemophilus influenzae nonserotype B	0 (0)	0 (0)	0 (0)	4 (7)
GBS	0 (0)	0 (0)	0 (0)	1 (2)
Viridans group *Streptococcus* spp.	0 (0)	0 (0)	0 (0)	1 (2)
None	0 (0)	6 (21)	6 (13)	26 (46)

GBS, group B *Streptococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphyloccus aureus*.

*$P(\chi^2) = 0.0003$ for *S. aureus* (MRSA and MSSA) vs. all other pathogens.

Table 3

Short-term outcomes for 102 pediatric patients with acute osteomyelitis with and without abscess formation

	Bone abscess (n = 25)	Muscle abscess (n = 29)	Any abscess (n = 46)	No abscess (n = 56)	P-value for any vs. no abscess
Number of event outcomes [n (%)][a,b]					
Septic emboli	3 (17)	4 (22)	6 (19)	2 (5)	0.13[1]
PICC required	13 (54)	16 (55)	27 (60)	18 (32)	0.0051[3]
Number surgeries	2 (1, 3)	2 (1, 3)	2 (1, 3)	<1 (0, 1)	<0.0001[2]
Readmission/relapse	5 (20)	2 (7)	6 (13)	2 (4)	0.14[1]
Readmission	5 (20)	2 (7)	6 (13)	2 (4)	-
Relapse	3 (14)	1 (4)	4 (10)	0 (0)	-
Imaging outcomes [median (Q1, Q3)][c]					
Number of MRI's ordered	1 (1, 1)	2 (1, 2)	2 (1, 2)	1 (1, 1)	0.0008[2]
Number of radiographs ordered	4 (3, 6)	4 (3, 5)	4 (3, 6)	3 (2, 4)	0.10[2]
Duration outcomes [median (Q1, Q3)][d]					
Total duration antibiotics	90 (56, 130)	52 (45, 102)	56 (47, 128)	45 (42, 55)	0.0004[2]
Total duration intravenous antibiotics	23 (12, 52)	24 (12, 47)	29 (12, 50)	9 (6, 31)	0.0002[2]
Total duration oral antibiotics	86 (35, 137)	34 (12, 84)	36 (23, 90)	35 (14, 41)	0.18[2]
Duration hospital stay (days)	16 (12, 24)	11 (9, 19)	13 (10, 21)	8 (6, 12)	<0.0001[2]
Time to defervesence	7 (2, 13)	4 (3, 8)	5 (2, 11)	1 (0, 3)	<0.0001[2]
Laboratory value outcomes [median (Q1, Q3)][e]					
Maximum CRP (mg/dl)	21.4 (13.2, 25.6)	14.2 (8.3, 24.3)	18.0 (10.1, 25.5)	6.1 (2.8, 15.2)	0.0002[2]
Maximum ESR (mm/h)	87.5 (71.0, 123.5)	96.0 (77.0, 115.0)	88.0 (68.0, 115.0)	50.0 (28.0, 73.0)	<0.0001[2]
Maximum WBC count (cells/ml)	15.0 (12.2, 18.7)	15.8 (11.62, 19.8)	14.8 (12.1, 19.3)	13.1 (10.7, 15.2)	0.02[2]

CRP, C-reactive protein; PICC, peripherally inserted central catheter; WBC, white blood cell.

[a] Compare P-values in this subset to Bonferroni-corrected type I error rate $\alpha = 0.05/4 = 0.013$.

[b] Total number without missing data for these outcomes (denominators): septic emboli (32 cases, 38 controls); PICC (45 cases, 56 controls); readmission (46 cases, 56 controls); readmission or relapse (46 cases, 56 controls); relapse (41 cases, 53 controls).

[c] Compare P-values in this subset to Bonferroni-corrected type I error rate $\alpha = 0.05/2 = 0.025$.

[d] Compare P-values in this subset to Bonferroni-corrected type I error rate $\alpha = 0.05/5 = 0.010$.

[e] Compare P-values in this subset to Bonferroni-corrected type I error rate $\alpha = 0.05/3 = 0.017$.

[1] P-value obtained from the Fisher exact test.

[2] P-value obtained from the Wilcoxon-rank sum test.

[3] P-value obtained from the χ^2-test.

Table 4

Late-onset complications of patients with and without abscess formation and at least 3 months of follow-up

Age (years)	Site of osteomyelitis	Abscess (bone or muscle)	Complications	Follow-up (months)
Abscess[a]				
14	Femur	Muscle	1	49
3	Humerus	Bone	2	3
17	Radius	Muscle	3	3
9	Fibula	Bone	4	11
6	Femur	Bone	5	84
15	Femur	Muscle	6	44
8.6	Metatarsal	Bone	7	110
11.6	Tibia	Bone	8	80
No abscess[b]				
5.3	Femur	NA	9	18
4.3	Femur	NA	10	62
0.8	Femur	NA	11	144

Complications: 1, leg-length discrepancy, persistent limp, avascular necrosis of the right femoral head; 2, pathologic fracture at the 3-month follow-up; 3, decreased range of motion of elbow; 4, abnormally wide physis, lost to follow-up; 5, 2.7 cm leg-length discrepancy, antalgic gait; 6, avascular necrosis and collapse of the femoral head; 7, growth retardation of the third (infected) metatarsal with secondary transfer metatarsalgia of the second metatarsal requiring osteotomy 108 months after diagnosis; 8, 1.7 cm leg-length discrepancy requiring epiphysiodesis 3 months after diagnosis; 9: chronic leg pain, osteonecrosis of the right femoral head; 10, 5 mm leg-length discrepancy, abnormal gait; 11, 6 mm leg-length discrepancy, chronic leg pain, avascular necrosis of the femoral head.

[a]Of 30 patients with at least 3 months of follow-up.

[b]Of 27 patients with at least 3 months of follow-up.