Diagnostic delay of pyogenic vertebral osteomyelitis and its associated factors

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Objectives: Pyogenic vertebral osteomyelitis (PVO) is a rare disease with possible severe complications (e.g. sepsis and spinal cord injury). In the 1990s, diagnostic delay (DD) was often extensive as PVO has a non-specific clinical spectrum, mostly afebrile with back pain, and access to magnetic resonance imaging (MRI) was not straightforward. Our aim was to perform a new study focusing on the clinical spectrum and DD of PVO and its associated factors.
Method: This study examined a prospective cohort of 88 patients having PVO with microbiological identification between 15 November 2006 and 15 November 2010.
Results: The 88 patients included in the study (female:male ratio 1:8) had a mean age of 64.1 years. The mean (sd) DD was 45.5 (50.4) days (range 2–280), and 46 patients (52.2%) were febrile at diagnosis. The main microorganism involved was *Staphylococcus* (n = 45; 51.1%). In univariate and multivariate analyses, age > 75 years, antecedent back pain, involvement of bacteria, topography of PVO, and anti-inflammatory drug intake did not affect the DD, unlike a C-reactive protein (CRP) value > 63 mg/L or a positive blood culture (DD lowered from 73 to 17 days and from 90 to 30 days, respectively). Conversely, X-ray investigation was associated with a longer DD (from 14 to 34.7 days). Severity at diagnosis was not significantly different depending on the intake of anti-inflammatory drugs.
Conclusions: Despite easier access to MRI, the DD for PVO remains long. One shortening factor is a high CRP value, which could be a useful diagnostic tool in case of back pain. Anti-inflammatory drugs seem to have no impact on DD and severity at diagnosis.

Pyogenic vertebral osteomyelitis (PVO) is a rare disease; its incidence is estimated at 2.4 per 100 000 inhabitants per year in high-income countries (1) and this value has risen in recent years (2, 3). Clinical diagnosis of PVO is challenging; only half of the patients are febrile and the most obvious symptom, back pain, is common in the general population (4). Nevertheless, a long diagnostic delay (DD) is associated with long-term complications such as chronic pain and stiffness, and could be a risk factor for spinal cord injury (5–9).

Confirmation of diagnosis requires a radiological examination. Magnetic resonance imaging (MRI) is the most sensitive and specific method of diagnosis, and the earliest positive examination. If contraindicated, a computed tomography (CT) scan is recommended (4–6). Thus, in case of suspicion of PVO, an MRI scan should be performed as soon as possible, standard X-ray being lately positive (4).

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In the 1990s, the mean delay for diagnosis of PVO was 70 days (10, 11). At that time, physicians expected this delay to be reduced in the future because of easier access to MRI (11). There are no recent data about evaluating current DD, describing the patients' medical history (from the first symptoms of PVO to the diagnosis), or the factors that could explain this delay (6).

In the current study we aimed to describe the medical history and DD of 88 patients diagnosed with PVO. In addition, we tried to identify the factors associated with a longer or shorter DD.

Method

We performed a prospective study describing the clinical history of 88 patients with PVO and their clinical, biological, and microbiological status at diagnosis. Patients were part of a multicentre, open-label, non-inferiority, randomized control trial studying antibiotic treatment duration in PVO (5). The patients in our study were the first 88 patients included in this trial in the two main recruiting centres (Raymond Poincaré University

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Hospital, Paris, and Tours University Hospital, France) between 15 November 2006 and 15 November 2010.

Inclusion criteria were: (1) suggestive clinical symptoms of PVO; (2) diagnosis of PVO assessed by MRI, a CT scan, and/or bone scintigraphy; and (3) reliable microbiological identification defined as a positive bacterial culture of at least one deep sample [blood culture or discovertebral biopsy (DVB)]. If the microorganism was a potential contaminant (coagulase-negative *Staphylococcus* and *Propionibacterium acnes*), two deep positive samples with a concordant identification were required.

Exclusion criteria were: undocumented PVO, non-pyogenic PVO (mycobacterial or fungal agents), or PVO on orthopaedic device.

Ethics

The protocol was approved by the French Data Protection Agency (CNIL) and the Institutional Review Board of Versailles University Hospital (authorization no. 06030). The study was performed in accordance with the ethical principles of the Helsinki Declaration and the Guidelines for Good Clinical Practice. Written informed consent for participation in the trial was obtained from all patients.

Data collection

Patients' characteristics (epidemiological data, medical history), radiological results (MRI and CT scan), and microbiological identification were collected prospectively. The absolute neutrophil count (ANC) and the C-reactive protein (CRP) dosages were recorded on the first day of hospitalization.

Anamnestic data since the beginning of symptoms were collected on admission to hospital, including: date of onset of symptoms; date of the first medical consultation; initial clinical presentation (fever defined as temperature > 38°C and presence of pain); and medical prescriptions of biological and radiological examinations (spine X-ray) prior to diagnosis. Non-steroidal anti-inflammatory drug (NSAID) and corticosteroid intake (without quantitative details) were recorded from patient and general practitioner interviews.

Past medical history of chronic back pain was recorded.

Definitions

Diagnostic delay (DD) was defined as the time (day) from the first symptoms to radiological diagnosis. Medical delay (MD) was the time (day) from the first medical appointment to diagnosis.

Objectives

The objectives were to determine the DD and MD in a prospective cohort of patients with microbiologically documented PVO, and identify the factors associated with shortened or extended DD.

Statistical analysis

Basic descriptive statistics (mean, median, and standard deviation) of DD and recorded variables were computed. The distribution of DD was not normal. Variables affecting DD were investigated with non-parametric comparison tests (Wilcoxon–Mann–Whitney and Kruskal–Wallis) or with regression of log-transformed DD on continuous variables.

The relative influence of variables of interest identified using these univariate tests was assessed with a regression tree and an analysis of variance (ANOVA). Residuals of the ANOVA were normally distributed.

All analyses were performed with R version 3.1.2 (R Core Team, R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria, 2014). Statistical significance was defined as $p < 0.05$.

Results

This study included 88 patients (65% males), with a mean age of 64 years. Population details, PVO characteristics, initial clinical presentation, and medical prescriptions are described in Table 1.

Blood culture was positive for 67 (76.1%) patients. *Staphylococci* spp. were involved in 51% (n = 45) of cases. One case of methicillin-resistant *Staphylococcus aureus* was recorded. *Streptococci* spp. were identified in 21.6% of cases (n = 19) and *Enterobacteriaceae* in 13.6% (n = 12).

PVO predominantly affected the lumbar and lumbosacral spine in 64.7% of cases (n = 57). Multiple localizations occurred in 14.8% of cases (n = 13).

Thirty-nine patients (44.4%) had received anti-inflammatory treatment between the onset of the symptoms and diagnosis: 25 (28.5%) had received NSAIDs and 14 (15.9%) corticosteroids. A spine X-ray before diagnosis was ordered for 40 patients (45%).

The mean value of CRP at diagnosis was 140 mg/L and the mean ANC was 9.6 G/L.

The mean time between the first symptom and the first medical consultation was 6 days; on average, 39 days were required between the first consultation and PVO diagnosis (MD). The mean DD (time elapsed since the onset of the first symptoms) was 45 days (median 31 days).

Factors associated with DD for PVO are presented in Table 2. Gender, age, and past history of back pain did not significantly impact DD ($p = 0.9$, $p = 0.4$, and

Table 1. Characteristics of the 88 patients with pyogenic vertebral osteomyelitis (PVO).

Age (years), mean ± sd (range)	64.1 ± 16.0 (26–95)
Male to female ratio	1.83
Antecedent, n (%)	
Chronic back pain	24 (27.3)
Acute back pain	13 (14.8)
Inflammatory rheumatism	3 (3.4)
Neoplasia	18 (20.4)
Diabetes	15 (17)
Neuropathy	8 (9.1)
Drug abuse	8 (9.1)
Dementia	2 (2.3)
Initial clinical presentation, n (%)	
Presence of initial pain	76 (86.4)
Presence of initial fever	46 (52.2)
Microorganisms, n (%)	
MSSA	29 (32.9)
CoNS	15 (17)
MRSA	1 (1.1)
Non-Enterococcal Streptococcus spp.	19 (21.6)
Enterococcus spp.	3 (3.4)
Escherichia coli	9 (10.2)
Klebsiella pneumoniae	3 (3.4)
Other*	11 (12.5)
Localization, n (%)	
Plurifocal	13 (14.8)
Cervical	19 (21.6)
Thoracic	20 (22.7)
Lumbar	45 (51.1)
Sacral	12 (13.6)
Medical prescriptions	
Pre-hospital prescriptions, n (%)	
NSAIDs	25 (28.5)
Corticosteroids	14 (9.15)
Spine X-ray	40 (45)
In-hospital prescriptions	
ANC (G/L), mean (range)	9.6 (2.45–22.1)
CRP (mg/L), mean (range)	140 (6–435)
Positive blood culture, n (%)	67 (76.1)
Medical consultation and delays	
Prior medical consultation, n (%)	88 (100)
Medical delay (days), median/mean ± sd (range)	23/39.2 ± 48.6 (2–280)
Diagnosis delay (days), median/mean ± sd (range)	31/45.5 ± 50.4 (2–280)

MSSA, Methicillin-sensitive *Staphylococcus aureus*; CoNS, coagulase negative *Staphylococci*; MRSA, methicillin-resistant *Staphylococcus aureus*; NSAID, non-steroidal anti-inflammatory drug; ANC, absolute neutrophil count; CRP, C-reactive protein; sd, standard deviation.

**Propionibacterium acnes* (n = 2), *Peptostreptococcus* (n = 2), *Citrobacter spp.* (n = 2), *Bacteroides fragilis* (n = 1), *Burkdolderia cepacia* (n = 1), *Aggregatibacter aprophilus* (n = 1), *Serratia marscecens* (n = 1), *Campylobacter fetus* (n = 1).

p = 0.5 respectively), neither did taking NSAIDs or corticosteroids (p = 0.052 and p = 0.8, respectively). In addition, the topography of PVO and the type of microorganism involved did not significantly impact the DD.

In the univariate analysis, initial fever before diagnosis was associated with a significantly shorter DD (decreased from 42 to 21 days, p = 0.006), as did a positive blood culture (DD decreased from 90 to 30 days, p < 0.001). Undergoing a spine X-ray examination was significantly associated with a longer DD, from 14 to 34 days (p = 0.04).

In the multivariate analysis, a level of CRP of 63 mg/L was identified as the cut-off value by regression tree analysis between long and short delays (mean DD of 73 days with CRP < 63 mg/L and 17 days with CRP > 63 mg/L; p = 0.001 when tested in a univariate comparison). An X-ray examination was associated with an increase in DD as in the univariate analysis.

In the multivariate analysis, a CRP value > 63 mg/L and positive blood cultures were the variables most significantly associated with early diagnosis according to the ANOVA (low p-values, p < 0.001).

Table 2. Factors associated with diagnostic delay (DD) during pyogenic vertebral osteomyelitis (PVO) with uni- and multivariate analysis.

	DD (days)		p-value	
	Present	Absent	Univariate analysis	Multivariate analysis
Age > 75 years	46.1 ± 38.3	45.2 ± 56.1	ns	ns
Antecedent back pain	36.5 ± 41.5	30.0 ± 29.6	ns	ns
Initial pain	30.0 ± 31.1	60.0 ± 40.3	0.058	0.003
Initial fever	21.0 ± 20.7	42.0 ± 41.5	0.006	ns
Positive blood culture	30.0 ± 31.1	90.0 ± 66.7	< 0.001	< 0.001
Bacteria involved			ns	ns
Localization			ns	ns
NSAIDs (n = 25)	40.0 ± 38.5	23.5 ± 26.7	ns	ns
Corticosteroids (n = 14)	25.5 ± 28.1	31.0 ± 32.6	ns	ns
Spine X-ray (n = 40)	34.7 ± 37.8	14.0 ± 14.8	0.04	0.02
CRP > 63 mg/L	17.0 ± 21.1	73.0 ± 55.5	< 0.001	< 0.001
ANC > 7.5 G/L	45.0 ± 61.0	15.0 ± 21.1	ns	ns

NSAID, Non-steroidal anti-inflammatory drug; CRP, C-reactive protein; ANC, absolute neutrophil count; ns, non-significant. Values given as mean ± standard deviation.

Discussion

To our knowledge, this is the only recent study focusing on DD for PVO and its associated factors since the generalization of MRI. The centres participating in the study have specific expertise in this field, so a bias should be expected. Nevertheless, the study population is consistent with the literature data regarding the gender, age, medical histories, and characteristics of PVO (localization and pathogens) (1, 4, 5).

PVO is rare but acute complications, possibly lethal, can occur (7, 12). Furthermore, if DD is more than 8 weeks, PVO can lead to chronic complications, altering the patient's functional status (8, 9). Establishing an early diagnosis may prevent these complications.

According to our study, all the patients had consulted a physician at least once before diagnosis. DD remains long (median 31 days) but seems shorter than in the 1990s (70 days) (10, 11). The period between first onset of symptoms and first medical consultation was short (6 days on average). Accordingly, we can hypothesize that DD is not due to the delay before medical interview but to the lack of suspicion of medical staff.

In our study we tried to identify factors associated with modified DD. Surprisingly, age is not significantly associated with a longer DD. Chronic back pain is frequent in the elderly, contributing to low suspicion in cases of PVO. One study found a DD longer than 3 months for the elderly (13). Nonetheless, in our study, DD was 45 days even in this population. Moreover, the proportion of back pain presentation was not significantly different in older than in younger patients (90% and 89%, respectively, p = 0.91).

NSAIDs and corticosteroids can modify the clinical presentation of PVO through several mechanisms: analgesic, antipyretic, and anti-inflammatory activity. Several studies have demonstrated a significant association between NSAID use and the spontaneously more severe presentation of bacterial infectious disease, with a reduced chemotactism of neutrophils shown in vitro (14, 15). However, the in vivo effect of NSAIDs on granulocyte function and cytokines is controversial, as it has previously been revealed that ibuprofen increases endotoxin-induced tumour necrosis factor (TNF)-α and polymorphonuclear leucocyte degranulation in vivo (16). A study on an experimental model found a worsening of the disease due to delayed diagnosis because the use of NSAIDs would mask the clinical warning signs, rather than inhibiting local inflammation (17). If NSAIDs or corticosteroids are prescribed, we should expect a longer DD. However, we did not find any significant difference between populations with NSAID intake vs. patients without NSAID intake (p = 0.052), and between patients with corticosteroid intake vs. patients without corticosteroid intake (p = 0.783).

Unfortunately, we did not study dosage and duration of treatment. A complementary study focusing on the duration of anti-inflammatory treatment would be of interest, because, despite not being significant (p = 0.053), it is near the limit.

We found a significant association between increased DD and a spine X-ray investigation, in uni- and multivariate analysis. We can hypothesize that a normal initial X-ray scan reassures the physician. According to European recommendations for non-specific low back pain in primary care, an X-ray scan should not be performed, but MRI is suggested in case of suspicion of a specific underlying pathology (18). The gold standard for radiological diagnosis when PVO is suspected remains spine MRI, although the results could be negative if it is performed too early (4, 19).

A CRP value over 63 mg/L was significantly associated with shorter DD in uni- and multivariable analysis (p < 0.001). Dosage of CRP during back pain symptomatology could increase suspicion of PVO and lead to a

decrease in DD. A positive blood culture was also significantly associated with a shorter DD (66–30 days ($p < 0.001$)) in uni- and multivariable analysis. Blood cultures are sensitive and efficient for the diagnosis (76% of PVO are bacteraemic) and should be performed for every suspicion of PVO.

Conclusions

The DD of PVO is still long in the 2010s (despite being shorter than during the 1990s) even with the generalized use of MRI. This may be explained by a low suspicion from physicians because of the low incidence of PVO and its non-specific presentation. The intake of anti-inflammatory drugs seems to have no effect either on DD or on severity at diagnosis, contrary to a high CRP value, which is associated with reduced DD. Therefore, the CRP level should be measured in patients presenting with back pain to investigate a possible PVO. These initial results need to be confirmed in a large-scale study.

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