Accuracy of serum LDH elevation for the diagnosis of *Pneumocystis jiroveci* pneumonia

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Summary

In 328 immunocompromised patients, 105 with and 193 without *Pneumocystis jiroveci* pneumonia (PCP), serum lactate dehydrogenase (LDH) was analysed retrospectively, taking into consideration the time interval from the onset of symptoms to the start of specific therapy. 97 of the 105 PCP patients were negative for human immunodeficiency virus (HIV). Eight were positive. Of the 193 patients without PCP 134 were HIV-negative and 59 were HIV-positive. In HIV-negative patients the sensitivity of LDH elevation was 63% and specificity 43%. In HIV-positive patients sensitivity was 100% and specificity 47%. The overall accuracy of LDH for the diagnosis of PCP was 52%, 51% in HIV-negative and 58% in HIV-positive patients.

Except for its sensitivity in HIV-positive patients, the value of LDH for the diagnosis of PCP should not be overestimated.

Abbrevations

BAL broncho-alveolar lavage
CR conventional x-ray
CT computed tomography
HIV human immunodeficiency virus
LDH serum lactate dehydrogenase
Li lithium
MDCT Multidetector computed tomography
PCP *Pneumocystis jiroveci* pneumonia
PJ *Pneumocystis jiroveci*
PCR polymerase-chain reaction
U unit

Introduction

Pneumocystis jiroveci pneumonia (PCP) remains a serious complication in immunocompromised hosts [1]. Features of PCP in human immunodeficiency virus (HIV)-negative immunocompromised patients differ significantly from those of HIV-related disease [2–4]. HIV-negative patients with PCP may have a lower organism burden in the lungs [5], often experience an abrupt onset of symptoms and a shorter duration of symptoms prior to seeking medical evaluation, and rarely develop cystic lung disease [2–4]. These observations suggest that host responses to *Pneumocystis jiroveci* (PJ) may be different, which may reflect differences in underlying immunodeficiency states [2, 3]. Thus extrapolation of the sensitivity of LDH for HIV-related PCP to HIV-negative patients may not be appropriate. LDH is a cytoplasmic enzyme present in all major organ systems. The extracellular appearance of LDH indicates cell damage or cell death [6]. Consequently, it is a very unspecific marker. In HIV-positive patients with atypical pneumonia, LDH elevation correlates well with the degree of lung tissue damage, and its sensitivity for PCP is reported to be up to 100% [6]. However, a review of the literature addressing the issue of serum LDH elevation in non-HIV PCP showed that to date no study dealing with this problem has been published. Indeed a reliable, sensitive and inexpensive test for non-HIV PCP would be of considerable clinical interest, especially considering the low sensitivity of conventional x-rays in the early phase of non-HIV PCP. The present study retrospectively analyses and compares both the sensitivity and specificity of serum LDH for PCP in patients with and without HIV infection.

Material and methods

All cases of broncho-alveolar lavage (BAL) – specimens analysed positive or negative for PCP – were identified retrospectively by reviewing microbiological records of the period 2006–2010. Patients tested positive could be additionally identified for the period 2002–2006. The test for *Pneumocystis jiroveci* (PJ) was performed by both polymerase-chain reaction (PCR) and by staining and microscopy in all cases.

Patients' records were reviewed for assessment of the underlying condition, the onset and duration of symptoms and the specific therapy given. The publication of patients' data was approved by our institutional review board.

Patients tested positive for PCP
Radiological and medical records documenting PCP on one or more thin-section computed tomographies (CTs) and PCP as a discharge diagnosis were reviewed respectively to confirm the diagnosis. PCP was confirmed by all 3 specialities (microbiology, radiology and infectiology) in all patients included. Serum LDH values were determined at least during the time interval from the onset of symptoms to administration of specific antibiotic therapy. Another criterion for inclusion was the absence of pulmonary co-infection or co-morbidity during the time period studied.

BAL was carried out on average 1 day after the first thin-section CT (range, one day before to 6 days after) and on average 0 days prior to or following LDH analysis (range 2 days before to 5 days after). The course of serum LDH was analysed with respect to elevation over the standard value and/or formation of a peak during the time interval from the onset of symptoms to the start of specific antibiotic therapy. A peak was defined as a high value which is higher than the average of all other values documented for the patient by 30%.

LDH analysis was performed photometrically from 2 ml li-heparin plasma per patient using the ADVIA 1800 system (Siemens Healthcare Diagnostics Eschborn). The reference range for this method is 120 U/L to 246 U/L, which is equivalent to the 95% confidence interval in healthy subjects. As the relative standard variance for this method has been calculated as 1–2% for our laboratory, the upper limit of the normal range for LDH at our institution is <250 U/L.

Chest CTs were obtained on multidetector (MD) CT scanners with 4, 16 or 64 detector rows (Somatom Sensation 4, 16 or 64, Siemens Medical Engineering, Forchheim, Germany). All images were reconstructed with 1 mm slice thickness. Initial and follow-up thin-section chest CTs were evaluated during routine and again retrospectively in an independent fashion by two trained observers (authors 1 and 7) in order to confirm or reject the diagnosis [3, 8, 9]. In case of discrepancy, decisions were reached by consensus. In patients with more than one CT an increase in pulmonary infiltrates before and/or regression after the administration of specific therapy was necessary to confirm PCP.

Patients tested negative for PCP
As the sensitivity of PCR from BAL specimens for the diagnosis of PCP is up to 100% [10], a negative PCR test was regarded as sufficient to rule out PCP. In patients tested negative more than once only the 1st episode was included. To be included in the group without PCP a patient had to be immunocompromised, to have a BAL specimen tested negative for PCP and at least one LDH value analysed between the onset of pulmonary symptoms and the start of specific therapy.

Statistics
In all patients calculations were performed using JMP IN 4.0 (SAS Inst. Inc. Cary NC 2003). In patients with PCP the duration of symptoms until LDH analysis was correlated with the LDH values by linear regression and the groups with normal and elevated LDH were compared regarding the duration of symptoms until LDH analysis by Student's t-test. A p-value <0.05 was regarded as significant.

Results

Data concerning all patients are listed on table 1.

Patients with PCP
A total of 189 patients with BAL specimens positive for PCP were identified. LDH values of the time interval from the onset of clinical symptoms to the start of therapy were available for 116 of the 189 patients. All patients but two had undergone chest CT. Of the remaining 114 patients 9 had to be excluded for suspected or proven co-infection or pulmonary co-morbidity, such as toxic lung damage due to medication (n = 1), transfusion-induced lung injury (n = 1), pulmonary aspergillosis (n = 3), cytomegalovirus (CMV) infection (n = 2), radiation-induced fibrosis (n = 1) or usual interstitial pneumonia (n = 1).

None of the remaining 105 PCP patients received specific inhaled or other antibiotic PCP prophylaxis at least 2 months prior to the onset of symptoms. 58 patients (55%) were already receiving broad-spectrum antibiotics at the time of diagnosis. The specific PCP treatment was sulfonamides (n = 57), atorvaquone (n = 21), clindamycin (n = 5), a combination of different antibiotics (n = 24) or pentamidine (n = 3). Additional corticosteroids were started (n = 39), continued (n = 46), added more than one week later (n = 5) or not used (n = 5).

The median time from the onset of the clinical symptoms to the first CT (CT1) was 5 (mean 9, range 0–61) days in all patients. 101 of the 105 patients had more than one CT during PCP. LDH profiles were available for a median time period of 463 days (mean 571, range 1–1672) in all patients. In 69 of the 105 patients (66%) LDH was above the normal level. It was elevated in 8 of the 8 HIV-positive (100%) and in 61 of the 97 HIV-negative patients (63%). In a total of 47 patients, 6 with normal and 41 with elevated LDH, the LDH profile showed a peak during PCP. In 35 patients there was more than one other episode of LDH elevation due to other reasons and in 10 patients LDH changes were not in any way correlated with the course of the infectious episode. In the 69 patients with elevated LDH the first pathological LDH value was measured a median time of 3 days after the beginning of clinical symptoms (mean 2 days before, range 80 days before to 80 days after). The median time from the onset of symptoms to the highest LDH value

was 6 (mean 10, range 0–55) days in the 47 patients with an LDH peak before the start of specific therapy. No significant correlation of the duration of symptoms and LDH values or elevation could be found. More results, including sensitivity of LDH elevation, are listed in table 2.

Patients without PCP

A total of 343 patients with BAL specimens negative for PCP were identified. LDH values for the time interval from the onset of clinical symptoms until the start of therapy were available for 217. 193 of these 217 patients had an obvious immunocompromising underlying condition, and were thus included in the study.

The results of patients without PCP including specificity of LDH elevation are listed in table 3.

Taking all patients together, LDH analysis produced a concordant result (elevation in patients with and no elevation in patients without PCP) in 155 of the 298 patients (52%). LDH values were in agreement in 39 of 67 HIV-positive (58%) and in 118 of 231 HIV-negative patients. Consecutively, the accuracy of LDH elevation for the diagnosis of PCP was calculated at 52% in all patients, 51% in HIV-negative and 58% in HIV-positive patients.

Discussion

In the early phase of PCP pulmonary infiltrates are often too slight to be depicted on the conventional x-ray (CR). Hence there is all the more demand for other inexpensive but sensitive diagnostic tools [11]. The sensitivity of LDH for the diagnosis of PCP has been repeatedly described as nearly 100% in HIV-positive patients [6, 12]. Hence all 8 HIV-positive patients in our study had elevated LDH values in the time from the onset of clinical symptoms to the start of specific therapy, confirming previous results. In HIV-negative patients, however, elevation of serum LDH yielded a sensitivity of only 64% in our study, regardless of the duration of disease until LDH analysis. In a way this appears to contradict a study by Festic et al. reporting LDH elevation in 29 of 30 patients with non-HIV PCP [13]. However, the study cited included only patients with advanced disease presenting with acute respiratory failure implying a high degree of tissue damage and cell death. Another study including 4 patients with collagen vascular diseases yielded a sensitivity of 100% and a good correlation of LDH with PCP activity as monitored on CR [14]. In our study all the patients included were referred for chest CT examinations which often revealed slight lung damage, too little to be depicted on CR. Consequently, much earlier stages of PCP were included in our patient cohort. As a longer duration of symptoms was correlated neither with higher LDH values nor with a higher ratio of elevated LDH-values, this does not completely explain discrepancies with existing literature data. As there may be differences in individual profiles and standard values, the sensitivity of a peak formation with and without elevation over the laboratory's standard value was considered in this study. The sensitivity of an LDH peak, however, was even lower

Table 1: Data of all patients			
	All patients	PCP-positive	PCP-negative
No. of patients	298	105	193
Male/female (n of patients)	168/130	62/43	106/87
Age (years)	17–82 (median 58; mean 56)	17–82 (median 62; mean 59)	22–82 (median 57; mean 55)
Duration of symptoms before LDH analysis (days)	1–84 (median 8; mean 10)	1–84 (median 7; mean 11)	1–42 (median 8; mean 9)
LDH elevation (n of patients)	176	69	107

Table 2: Patients with PCP and sensitivity of LDH			
Underlying diseases of the 105 patients with PCP	n (%)	LDH elevation n (%)	sensitivity of LDH in %
Haematological malignancies	52 (50)	30/52 (58)	58
with stem cell transplantation (mean 490, range 31–878 days before)	7 (7)	4/7 (58)	58
Collagen vascular diseases	18 (17)	16/18 (89)	89
Solid tumors	16 (15)	8/16 (50)	50
Solid organ transplantation	10 (9)	7/10 (70)	70
HIV infection	8 (8)	8/8 (100)	100
Congenital immunodeficiency syndrome	1 (1)	0/1 (0)	0
All patients	105	69/105 (66)	66

Table 3: Patients without PCP and specificity of LDH			
Underlying diseases of the 193 patients without PCP	n (%)	LDH elevation n (%)	Specificity of LDH in %
Haematological malignancies	89 (46)	63/89 (71)	29
with stem cell transplantation (mean 224; range 20–378 days before)	8 (4)	4/8 (50)	50
Collagen vascular diseases	6 (3)	2/6 (33)	66
Solid tumors	30 (16)	7/30 (23)	77
Solid organ transplantation	7 (4)	4/7 (57)	43
HIV infection	59 (31)	31/59 (53)	47
Severe anorexia nervosa	2 (1)	0/1 (0)	100
All patients	193	107/193 (55)	45

than that of an elevation alone. All in all the sensitivity of LDH elevation for PCP was 67%, 64% in HIV-negative and 100% in HIV-positive patients. Thus a negative LDH level does not exclude acute PCP in HIV-negative immunocompromised patients. A previous study in HIV-positive patients showed that LDH does not qualify as a specific marker for PCP [12]. This was confirmed by our evaluation for both HIV-positive and HIV-negative patients. The lack of specificity of LDH is chiefly explained by its ubiquitous intracellular prevalence [6]. In conclusion, in HIV-negative patients in particular more accurate diagnostic tools, such as BAL and CT, should be used for the diagnosis of PCP. Further, except for its sensitivity in HIV-positive patients, the value of LDH for the diagnosis of PCP should not be overestimated.

Limitations

Our study has several limitations: to be considered in the first place is the retrospective setting. LDH had not been quantified in all patients whose BAL specimens were analysed for PJ. On the other hand an elevated LDH level may have strengthened suspicion of PCP and prompted the quest for PJ in BAL specimens. This might have weakened the retrospectively calculated specificity of LDH. Moreover, the duration of symptoms, which is recorded retrospectively in the majority of studies, is even more prone to inaccuracy in a prior retrospective setting. Thus a prospective study would be desirable to confirm our results.

Study funding / potential competing interests

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