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SHORT REPORT

The interpretation of zinc protoporphyrin changes in lead intoxication: a case report and review of the literature

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Background	Zinc protoporphyrin (ZPP) has been used both as a screening and diagnostic test for overexposure to lead for nearly 30 years, although limitations for both purposes are recognized.
Methods	We present longitudinal findings for ZPP and whole-blood lead in a man with two episodes of acute lead intoxication and review the literature on the use of ZPP.
Results and conclusions	ZPP elevations in both chronic and acute exposure settings lag behind elevations in whole-blood lead by ~8–12 weeks. Therefore, ZPP measurement, in conjunction with whole-blood lead determination, has clinical utility in cases of substantial overexposure by providing information on how long an individual may have been overexposed to lead. A guide to the interpretation of various combinations of whole-blood lead and ZPP results is provided. However, while ZPP levels do correlate with whole-blood lead measurements in aggregate, the considerable individual variability of ZPP measurements, poor sensitivity at lower ranges of lead exposure, poor specificity and delayed changes in unstable exposure conditions indicate that this test contributes little to screening programs. Finally, our results confirm that basophilic stippling is seen in acute as well as chronic lead intoxication, and may provide the first indication of lead intoxication.
Key words	Basophilic stippling; lead poisoning; zinc protoporphyrin.
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Introduction

Zinc protophyrin (ZPP) was proposed as a simple screening test for lead intoxication in 1974 by Lamola and Yamane [1]. With the subsequent development of a portable hematofluorometer three years later, rapid, inexpensive, field-testing of occupationally exposed groups became possible on a wide scale [2]. Shortly thereafter, ZPP testing became a legal requirement in the surveillance programs of workers occupationally exposed to lead in the USA [3]. Nevertheless, despite extensive application for almost 30 years, conflicting reports on the utility and interpretation of ZPP can be found in the literature [4–9]. Furthermore, data on ZPP findings for acute lead intoxication are limited. We report serial laboratory findings from a recent case of acute lead poisoning, review the literature on acute and chronic lead poisoning and ZPP, and provide a method for the interpretation of ZPP and whole-blood lead results.

Case report

The patient was a 30-year-old male referred to our clinic for assessment of a whole-blood lead of 3.9 μmol/l (79.9 μg/dl) drawn by his primary care physician. He was employed as a torch cutter in an outdoor scrap metal yard. He had been performing these duties for 13 months. Approximately 3 months prior to

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presentation, he had begun to cut painted bridge beams. He wore a dust mask only and no lead monitoring program was present in the workplace.

His chief complaint was a 1 year history of cough productive of grayish mucus, which improved when away from work. On review of systems, he reported a mild headache, fatigue, light-headedness and past episodes of colicky abdominal pain not present at the time of presentation. He denied arthralgias and parasthesias. No previous lead values were available and no other non-occupational sources of lead exposure were identified. His past medical history was significant for binge alcohol consumption and two episodes of kidney stones predating his reported lead exposure.

He was removed from work but not treated with chelation. Figure 1 shows the whole-blood lead and ZPP values after the first presentation. The employer and relevant authorities were contacted and a lead surveillance program was instituted at the workplace. The patient returned to work in a position not involving direct work with lead. At that time, his blood lead was 2.4 μmol/l (50 μg/dl). Further follow-up was arranged with his local physician.

Nineteen months after his first presentation, the patient presented to his family physician with a 2 week history of irritability, diffuse myalgias and arthralgias, most marked in the right knee. He had resumed torch cutting of bridge beams 3 weeks prior to presentation and, although he had been supplied with appropriate respiratory protection, he suspected it was not functioning properly. A whole-blood lead was drawn with a result of 6.4 μmol/l (132.8 μg/dl). He was immediately referred back to our clinic and admitted for treatment. On initial physical examination, he was awake and alert. His abdomen was non-tender and his reflexes were brisk. An extensive initial laboratory investigation was otherwise within normal limits, except for a blood smear showing basophilic stippling (Figure 2). He was treated for 5 days with i.v. chelation with EDTA followed by 10 days of oral chelation with succimer, which produced a rapid resolution of symptoms. The laboratory values for this episode are presented graphically in Figure 3.

The ZPP level peaked 2 weeks after the first presentation (~14 weeks after the onset of exposure) and remained elevated for 12 weeks. After the second presentation, at which time chelation therapy was instituted, the ZPP was initially normal despite a markedly elevated lead, peaked at ~3 weeks after presentation (6 weeks after the onset of exposure) and remained elevated for ~10 weeks. The absence of a rebound in blood lead levels following the completion of chelation therapy is further evidence of the acute nature of exposure and the lack of a significant body burden of lead.

Discussion

The exposure history and laboratory findings indicate that this man experienced two episodes of acute overexposure to lead. In the first presentation, overexposure

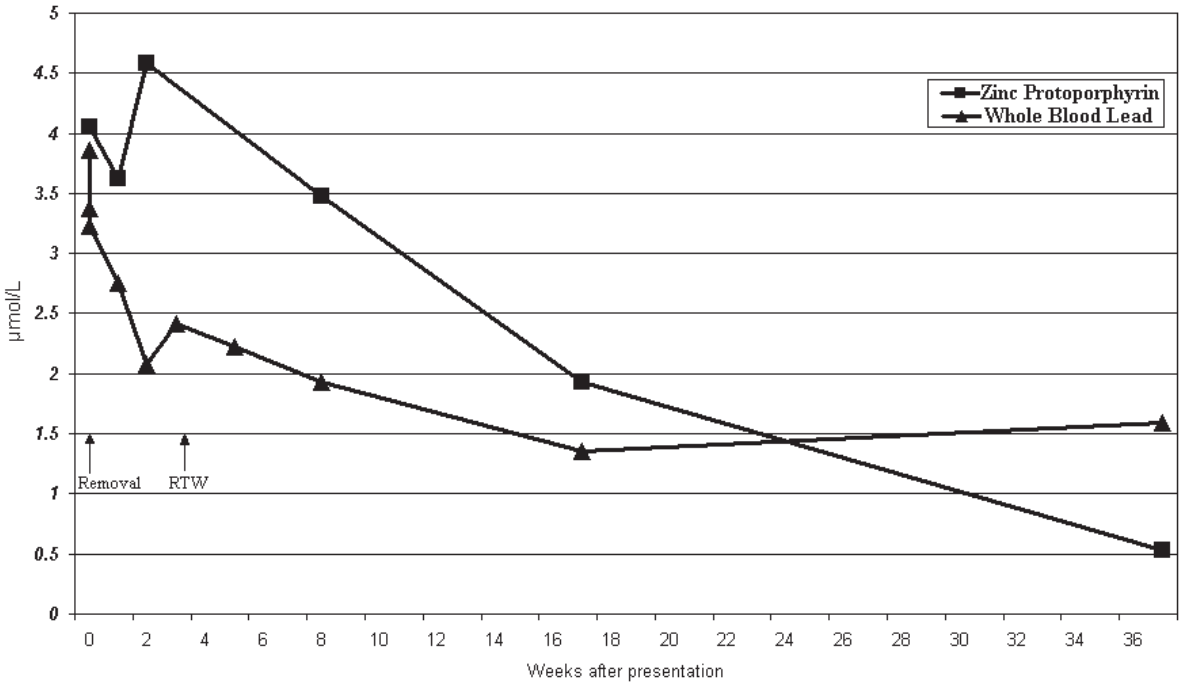

Figure 1. Initial presentation, treatment by removal alone.

began at most 12 weeks prior to presentation. The rapid fall in whole-blood lead levels following removal from work and without chelation therapy also suggests that the overexposure was of short duration. The evidence that he experienced symptomatic lead intoxication at first presentation is equivocal.

In the second episode, the exposure to lead was likely greater and began ~3 weeks prior to presentation. At that time, he had obvious symptoms and signs consistent with lead intoxication.

These findings are consistent with other case reports of acute lead poisoning in which blood lead levels are elevated but with normal ZPP values at presentation [10,11]. The same finding has been described in children following lead ingestion [12,13]. Based upon experimental studies in volunteers ingesting lead, the delay in the initial elevation of ZPP may vary from 0 to 21 days [14,15]. The importance of this observation is twofold: ZPP measurement can provide important temporal information on the duration of overexposure to lead. However, this also means that for screening purposes, ZPP measurements will not be able to detect acute overexposure to lead for days to weeks.

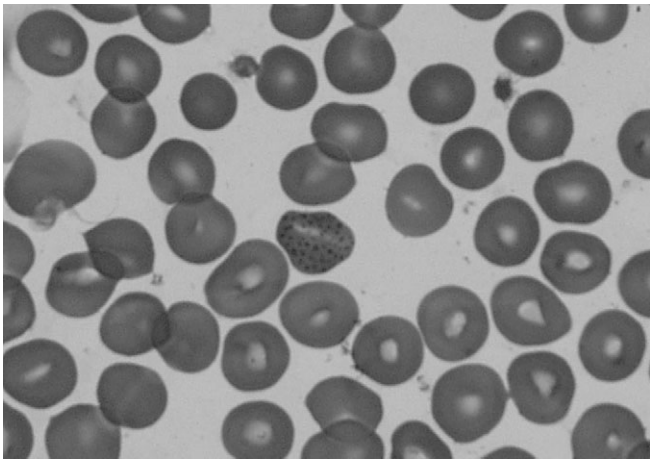

Figure 2. Light microscopy of blood smear demonstrating erythrocyte with basophilic stippling.

A similar phenomenon has also been documented in cases of chronic overexposure. In a prospective study of newly exposed workers, steady-state levels of ZPP lagged behind those of blood lead by 3–6 months [16]. Lerner *et al.* [5] studied a group of 101 smelter workers who had had no exposure for 10 weeks due to a strike. The mean blood level on leaving the workplace was 2.8 μmol/l (57 μg/dl) which had fallen to 1.8 μmol/l (37 μg/dl) by the time of re-exposure. The mean ZPP at the time of re-exposure was 95 μg/dl blood, with mean values of 94, 81, 91, 145 and 134 μg/dl at 2, 6, 10, 35 and 50 weeks following re-exposure. Note that ZPP values fell for the first 6 weeks of re-exposure, reflecting the prior 10 week period of work stoppage.

This delay is consistent with the biological basis for ZPP alterations. Lead interferes with heme synthesis in

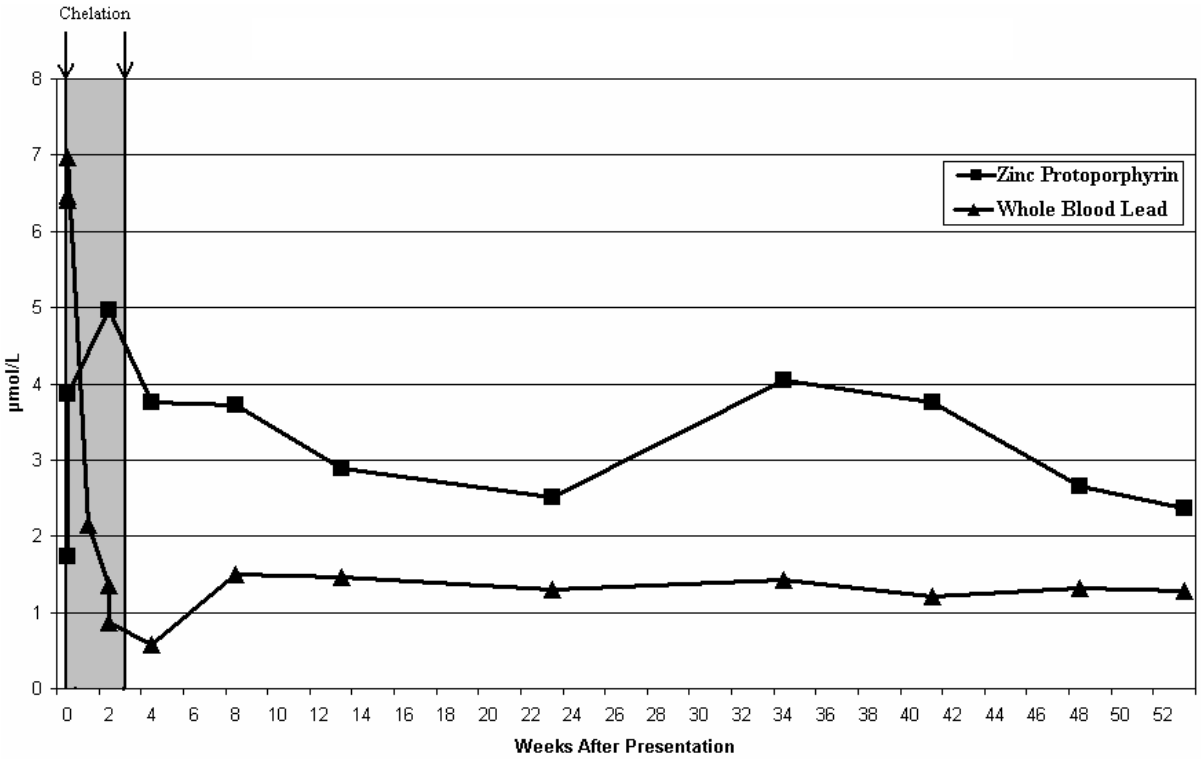

Figure 3. Second presentation: treatment by i.v. and oral chelation.

part due to inhibition of the enzyme ferrochelatase, which catalyzes the incorporation of iron into protoporphyrin IX to form heme. Protoporphyrin therefore accumulates in erythrocytes, with the majority binding to zinc and remaining present for the lifespan of the erythrocyte [17]. Accordingly, elevations in ZPP depend upon the number of erythrocytes in which heme synthesis has been inhibited compared with normal erythrocytes. Since the normal erythrocyte life span is reduced as a consequence of lead intoxication, ZPP elevations following lead exposure will theoretically plateau somewhat less than 120 days under stable conditions. By the same reasoning, ZPP declines following cessation of excessive lead exposure will lag by a similar interval. This decrease has been noted to be further attenuated when exposure has occurred over a more prolonged period of time, presumably due to a higher body burden of lead [6].

Early studies reporting on the utility of ZPP with relation to blood lead are difficult to interpret, as they did not account either for this temporal difference or unstable exposure conditions, since a cross-sectional design was used without information on the length of exposure [18]. Some early investigators concluded that measuring ZPP may be a better method than measuring blood lead levels for screening purposes, as a better correlation between ZPP levels with most symptoms and clinical abnormalities, including anemia, was observed [19]. However, more recent studies have presented conflicting findings on the association between ZPP and hemoglobin levels [8]. Similarly, a recent study found that while ZPP levels were correlated with overall symptoms, no association was observed with lead-related symptoms [20].

While ZPP values did correlate overall with blood lead in these earlier studies, a large amount of individual variability is apparent in the data. Subsequent studies have confirmed this finding [6,9].

Early studies were generally performed on occupational groups with higher exposures and correspondingly higher lead levels. A consensus has emerged that ZPP is insensitive at lower lead levels and should not be a component of screening programs [21,22].

The specificity of ZPP is poor. There are alternative causes of an elevation in ZPP, which should be considered particularly when the blood lead level is normal [23–28]. Several of these causes are listed in Table 1, which provides a summary of the interpretation of ZPP and lead results. Falsely elevated ZPP findings have also been shown to result from elevations in bilirubin and, to a lesser extent, carboxyhemoglobin [29,30].

Our case report demonstrates that with chelation, ZPP levels remain elevated for a prolonged period of time, even when blood levels have fallen. We conclude that ZPP therefore has no role in monitoring treatment efficacy. This finding is consistent with a case series of nine patients treated with oral penicillamine following occupational lead intoxication [7]. However, ZPP may have a role in detecting the surreptitious use of chelation in order to lower the blood lead and avoid medical removal from the workplace.

Table 1. Interpretation of Lead and ZPP findings

Zinc protoporphyrin	Whole-blood lead	
	Normal	Elevated
Normal	Normal	Acute overexposure to lead
Elevated	Iron-deficiency anemia [23] Sickle cell anemia [24] Sideroblastic anemia [25] Anemia of chronic disease [26] Chelation therapy Erythropoietic protoporphyria [27] Vanadium exposure [28]	Chronic overexposure to lead

Basophilic stippling is generally considered to be an unreliable indicator of lead intoxication, largely on the basis of poor specificity, with one study finding it to be present in 27% of consecutive internal medicine patients without lead exposure [31], but also poor sensitivity when blood lead levels are below ~4.8 μmol/l (100 μg/dl). Our case confirms that this finding can be observed in acute as well as chronic lead intoxication. In other case series, it has been the first indicator of lead intoxication [11].

In summary, we believe that ZPP has no role in screening programs because of poor sensitivity, poor specificity, high individual variability, a lag in changes when exposure is unstable and conflicting data on the correlation with other biological indicators. Reasons to perform this test should be to distinguish between acute and chronic lead intoxication or to detect the surreptitious use of chelation.

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