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SHORT COMMUNICATION

Absence of recognition of low alkaline phosphatase level in a tertiary care hospital

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Abstract
Summary Low serum total alkaline phosphatase level (ALP), the hallmark for hypophosphatasia (HPP), must be recognized to provide appropriate care of the patients and to avoid antiresorptive treatment. The prevalence of persistent low ALP in a clinical setting is 0.13 % and the recognition is very low (3 %).
Introduction A low serum total alkaline phosphatase level is the hallmark for the diagnosis of hypophosphatasia. Although very rare, HPP must be recognized to provide appropriate treatment of non-union fractures and to avoid potentially harmful drugs, such as antiresorptive treatments. The aim of this study was to assess the recognition of persistent low ALP in a tertiary care hospital.
Methods Between the 1st of January and the 31st of December 2013, 48,755 patients had ALP assessment in the Biochemistry Department of our hospital. Sixty-eight patients had all serum ALP values persistently below 40 IU/l. Among them, six had potential causes of secondary hypophosphatasia. We consulted the summary discharges of the 62 patients in order to check for the notation of low ALP. Patients from the departments of rheumatology and internal medicine were contacted to fulfill a questionnaire about clinical manifestations potentially related to HPP.
Results 0.13 % of hospitalized patients had persistently low value. They were 46.5±17.7 years old, and 73 % were females. The low ALP value was notified in the discharge summary for two patients (3 %), without any comment. Twenty-four patients (46 +/-16 years old) were contacted. Eight patients had fractures; two had a diagnosis of rickets in the childhood; two had symptomatic chondrocalcinosis. Nine had dental abnormalities. Three were receiving a bisphosphonate; two of them had a fracture while being treated with bisphosphonate.
Conclusion Our study shows that low ALP is not recognized in a clinical setting in adults hospitalized in a tertiary care hospital.

Keywords Alkaline phosphatase level · Bisphosphonate · Hypophosphatasia · Osteomalacia

Introduction

A low serum total alkaline phosphatase (ALP) level, associated with clinical and radiographic findings, is the hallmark for the diagnosis of hypophosphatasia (HPP). HPP is an inborn loss-of-function mutation within the gene ALPL that encodes the cell surface enzyme tissue nonspecific isoenzyme of ALP. It is a rare disorder with an estimated prevalence between 1/100,000 and 1/300,000 in severe forms and 1/6370 in moderate forms [1, 2]. The childhood form of the disease is characterized by ricket-related deformities of the skeleton, craniosynostosis, delays in walking, short stature, fractures and bone pain, and early teeth loss [3]. The diagnosis of adult forms of HPP is a challenge; patients typically present in middle age with recurrent poorly healing metatarsal stress fractures or

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atypical diaphyseal subtrochanteric femoral fracture; they have also an increased risk of chondrocalcinosis, enthesopathies with ossifications, and even calcific periarthritis [4–6]. However, the severity of the disease is associated with the early age at onset; adult forms may be mild with highly variable clinical expression and are easily overlooked.

Although very rare, hypophosphatasia must be recognized to provide appropriate treatment of non-union fractures and chronic bone pain and to avoid worsening osteomalacia by using potentially harmful drugs, such as antiresorptive drugs used to treat osteoporosis and non-traumatic fractures [7, 8]. The primary clinical utility of ALP assessment is the diagnosis of osteomalacia, Paget's disease, and other bone diseases with high-bone turnover based on an increased ALP value. Less attention is paid to the low values of ALP.

The aim of this study was to assess the recognition of persistent low ALP. We used values obtained as part of medical care in a population of hospitalized adults in a tertiary care hospital.

Study population

Patients were selected from the records of the Biochemistry Department of our hospital. We excluded patients for whom the ALP assessment was performed in the emergency department, as stress can be associated with low ALP [9]. Between the 1st of January and the 31st of December 2013, 48,755 patients had at least one ALP assessment. We selected (Fig 1) patients having at least one value below the threshold of 30 IU/l, and then, among them, those having several assessments of ALP with at least 1 below 30 IU/l, and all others below 40 IU/l, in order to reduce the likelihood of analytic error. Those having occasionally normal value (i.e., higher than 40) were considered as fluctuating. Thus, 68 patients had all serum ALP values persistently below 40 IU/l. Among them six had potential causes of secondary hypophosphatasia [5]: massive thoracic surgery (n=2), acute disease in intensive care (n=2), and cancer with chemotherapy (n=2).

After authorizations were given, we consulted the summary discharges of the 62 patients in order to identify notation of low ALP; absence of recognition was defined by the absence of notation of low ALP on the discharge summary.

Patients from the departments of rheumatology and internal medicine were contacted to fulfill a standardized questionnaire about skeletal manifestations potentially related to HPP. The questionnaire was completed either on a telephone interview or during an outpatient visit.

Results

In 2013, 0.13 % of hospitalized patients having several assessments of ALP, had persistently low value, below 40 IU/l (Fig. 1). They were hospitalized in the departments of rheumatology (n=17), internal medicine (n=13), endocrinology (n=14), gastroenterology (n=9), and others (one to three patients in each). The main reason for hospitalization, as reported in the discharge summary, was inflammatory rheumatic disease (n=10), connective tissue diseases (n=7), viral or metabolic hepatitis (n=6), and miscellaneous (n=39). . None of the primary reasons for hospitalization was a clinical symptom typically related to HPP. None of them were from the orthopedic surgery department. They were 46.5±17.7 years old, and 73 % were females. The low ALP value was notified in the discharge summary for the two patients, without any comment, i.e., 3 % of patients.

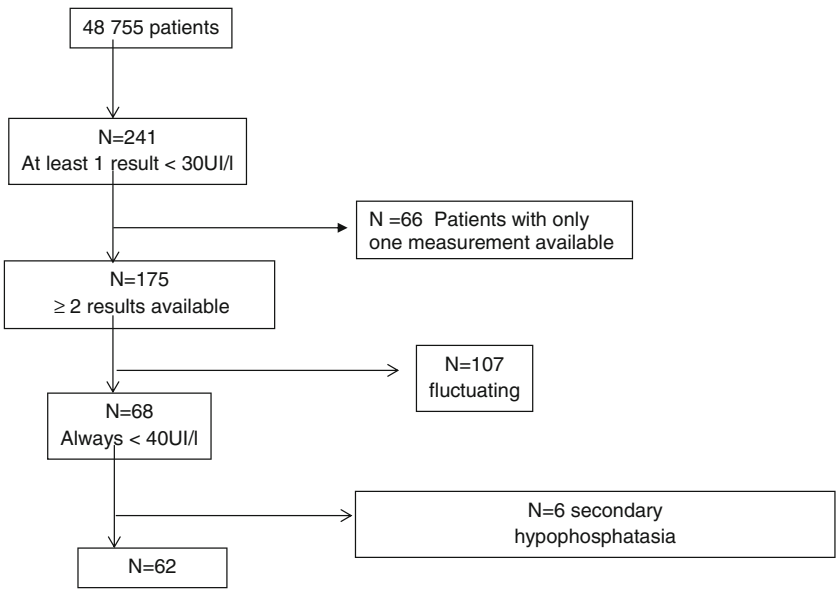

Fig. 1 Flow chart

Among the 62 patients, 25 were from the rheumatology or internal medicine departments; 24 patients (20 females, four males) gave their consentment for being contacted. They were 46±16 years old. Results of the questionnaires dedicated to symptoms potentially related to HPP are reported in Table 1. Eight patients (seven females) had fractures (metatarsus, vertebra, tibia, humerus, wrist, elbow, rib, ankle); none had femoral fracture; two patients recalled having a diagnostic of rickets in the childhood, but considered themselves unaffected by a skeletal disease in early adulthood; two patients reported healing delay of fractures. Two patients (37 and 56 years old), both female, had symptomatic chondrocalcinosis.. A number of dental abnormalities were reported by the patients (Table 1).

Three of the 24 patients were receiving a bisphosphonate, for prevention of corticosteroid-induced osteoporosis [2] and fracture [1], although low ALP was present before the initiation of both the corticosteroids and the antiresorptive treatments. Two of these patients had a fracture while being treated with bisphosphonate (1 vertebra, 1 wrist).

Discussion

Our study shows that low ALP (persistently below 40 IU/l) is not recognized in a clinical setting in adults hospitalized in a tertiary care hospital. The 0.13 % prevalence in our population is higher than the 0.06 % prevalence reported recently in a large, rural, and multispecialty clinic population using as a threshold a persistent value of ALP below 30 IU/l [5]. Our prevalence is dramatically higher than the prevalence of hypophosphatasia as a disease, and our result must be interpreted cautiously. We dealt with a laboratory abnormality, not with a disease, as we did not perform genetic testing of HPP. However, we observed that a proportion of patients with persistent low ALP levels have symptoms similar to those of the adult form of HPP. The proportion of patients with past fractures was 33 %, which is similar to the proportion reported in McKiernan's study (30 % of patients with past fractures, mean age 46.5). Two females had chondrocalcinosis; one of them was unexpectedly young (36 years old). We observed a higher proportion of women in our cohort, in accordance with

Table 1 Clinical characteristics potentially related to hypophosphatasia in adults with persistent low ALP

Patient	Age	Sex	Rickets in child hood (Reported by the patient)	Familial history of HPP	Diagnosis	History of Fractures	Chondro-calcinosis	Dental abnormalities	Bisphosphonate
1	42	Female	Yes	No	Sjogren syndrome	10	No	Yes (TE)	No
2	37	Female	No	No	Sjogren syndrome		No	Yes (TE)	No
3	24	Female	No	No	Lupus		No	Yes (ELDT)	No
4	36	Female	No	No	APLS	2 (humerus)	No	No	No
5	46	Female	No	No	ANCA vasculitis		No	No	No
6	62	Female	No	No	Cystoid macular edema		No	No	No
7	67	Female	No	No	Antisynthetase syndrome	3 rib, 1 vertebra	No	No	Yes *F
8	41	Female	No	No	Degenerative disk disease		No	No	No
9	22	Female	No	No	Chronic inflammatory arthritis		No	No	No
10	22	Female	No	No	RA		No	No	No
11	64	Female	No	No	RA	3 rib	Yes	No	Yes
12	51	Female	No	No	RA		No	Yes (SDA, GR)	No
13	36	Female	No	Yes	RA	2 tibia	Yes	Yes (GR, MT)	No
14	33	Female	No	No	SPA		No	No	No
15	56	Female	No	No	SPA	1 elbow	No	No	No
16	43	Female	No	No	SPA		No	Yes (dental fracture)	No
17	34	Female	No	No	Scleroderma	1 tibia	No	No	No
18	73	Female	No	No	Giant cell arthritis		No	No	Yes*F
19	72	Female	No	No	RA		No	No	No
20									
21	53	Male	No	No	Primitive cerebral vasculitis	2 tibia, clavicle	No	Yes (TE)	No
22	59	Male	Yes	No	Severe osteoarthritis		No	Yes (SDA,TE)	No
23	61	Male	No	No	Chronic inflammatory arthritis		No	Yes (TE)	No
24	24	Male	No	No	Uveitis		No	No	No

RA rheumatoid arthritis, SPA spondyloarthritis, *APLS* antiphospholipid antibody syndrome, *ANCA* anti-neutrophil cytoplasmic antibodies, *TE* teeth enamel (abnormalities of), *ELDT* early loss of deciduous teeth, *SDA* spontaneous dental avulsion, *GR* gingival recession, *MT* mobile teeth, **F* fracture during antiresorptive drugs

other studies [4, 5]. These results were obtained in a selected population of patients, i.e., those hospitalized in departments of rheumatology and internal medicine; this increases the probability to find musculoskeletal symptoms. We did not assess the presence of these symptoms in patients from other departments of our hospital.

A high number of our patients had a fluctuating value; the ALP measurement is reliable and reproducible, explaining our choice to exclude these patients. ALP may increase after a fracture. That means that several assessments might be necessary in some patients with symptoms suggestive of HPP. A number of diseases may be associated with persistently or transiently low value of ALP [5] which normalizes with treatment of the underlying disease [10–12]. Low ALP value is a rare feature, but may have a higher prevalence than previously recognized. Attention must be paid to this parameter, to provide appropriate treatment of non-union fractures, and chronic bone pain, and to avoid worsening of osteomalacia. Its recognition could help to prevent complications related to such antiresorptive drugs and/or physiologic changes [8], with serious complications in previously undiagnosed patients.

Compliance with ethical standards

Conflicts of interest E. Maman, D. Borderie: No disclosure.

C. Roux: Research grants and/or honoraria from Alexion, Amgen, Bongrain, MSD, Lilly.

K. Briot: Research grants and/or honoraria from Amgen, MSD, Lilly, Pfizer.

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