Bone marrow aspirate: a diagnostic tool for primary hyperoxaluria type 1

Apport de la ponction sternale dans le diagnostic de l'hyperoxalurie primaire de type 1

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Abstract

Introduction: Type1 primary hyperoxaluria is an infrequent autosomal recessive metabolic disease characterized by the accumulation of calcium oxalate in the kidney, which leads to end stage renal disease. In fact, the diagnosis of this disease is mandatory in order to avoid graft loss.

Aim: To assess the incidence of primary hyperoxaluria and to develop the diagnostic value of bone marrow infiltration by calcium oxalate in uremic stone former patients.

Methods: This study was conducted on a cohort of stone former patients identified in the south of Tunisia over a period of 18 years. Baseline characteristics were recorded. Clinical and laboratory data were collected on chart review. Secondary forms of hyperoxaluria were excluded. Bone marrow aspirate was performed in uremic patients from this cohort because early hyperoxaluria was suspected. Diagnostic accuracy of this test relating to sensitivity, specificity, positive predictive value and negative predictive value were also calculated.

Results: A cohort of 31 patients comprising 17 male patients and 14 female patients were identified. During this time of diagnosis, the patient's ages ranged from 9 to 57 years old and 22 of them (70%) unfortunately died. Bone marrow aspirate was safely done in 16 uremic patients. It was positive in 12 patients and negative in 4 patients. Sensitivity, specificity, positive predictive value and negative predictive value were respectively 85%, 100%, 100% and 50%.

Conclusion: The bone marrow examination represents both an easy and a worldwide feasible solution for the diagnosis of oxalosis, which affords an early diagnosis.

Key words: Bone marrow aspirate - Chronic renal failure - Oxalosis.

Résumé

Introduction: L'hyperoxalurie primaire de type 1 est une maladie métabolique autosomique récessive peu fréquente caractérisée par l'accumulation d'oxalate de calcium dans les reins entrainant une insuffisance rénale terminale. Le diagnostic précoce est primordial afin d'éviter la perte du greffon.

Objectif : Evaluer l'incidence de l'hyperoxalurie primaire et d'étudier la valeur diagnostique de l'infiltration médullaire par l'oxalate de calcium chez des patients urémiques lithiasiques.

Méthodes: Cette étude a été menée sur une cohorte de patients identifiés lithiasiques dans le sud tunisien sur une période de 18 ans. Les données clinico-biologiques ont été recueillies à partir des dossiers. Les formes secondaires d'hyperoxalurie ont été exclues. Une ponction strenale a été réalisée chez les patients urémiques de cette cohorte devant la suspicion d'oxalose. La précision diagnostique de ce test représentée par: la sensibilité, la spécificité, la valeur prédictive positive et la valeur prédictive négative a été calculée.

Résultats: Une cohorte de 31 patients comprenant 17 hommes et 14 femmes a été colligée. Pendant cette période d'étude, l'âge des patients variait de 9 à 57 ans et 22 d'entre eux (70%) sont décédés. La ponction sternale a été réalisée chez 16 patients urémiques. Elle était positive chez 12 patients et négative chez 4 patients. La sensibilité, la spécificité, la valeur prédictive positive et la valeur prédictive négative étaient respectivement de 85 %, 100 %, 100 % et 50 %.

Conclusion: La ponction sternale représente un outil facile et applicable pour le diagnostic précoce de l'oxalose.

Mots clés : ponction sternale, insuffisance rénale terminale, oxalose.

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INTRODUCTION

Primary hyperoxaluria type 1 (PH1; MIM 259900) is a rare autosomal recessive metabolic disease caused by hepatic, peroxisomal alanine, glyoxylate aminotransferase (AGT) (E.C. 2.6.1.44) deficiency involved in glyoxylate detoxification (1–3). In point of fact, it is biochemically characterized by the overproduction of oxalate and glycolate and clinically characterized by the deposition of insoluble calcium oxalate, not only initially in the kidneys as urolithiasis and/or nephrocalcinosis, but also following renal failure throughout the body especially in the bone marrow(4–6). The pathogenesis of the disease is caused by mutations in the AGXT gene (MIM 604285) encoding the AGT (7,8). Although this disease is extremely heterogeneous at the clinical level and although substantial advances in its control have been recently made (8), patients are still vulnerable to death due to untreated end-stage renal disease (ESRD) either in the early infancy, in adolescence or, even, in adulthood in the developing countries(7,8). Accordingly, its management is a major example of the technical, ethical, epidemiological and financial dilemmas raised by recessive life-threatening diseases. Therefore, Oxalosis could be considered as one of the rare conditions where therapeutic withdrawal might be an acceptable option in case of low income and local resources(8,9). Additionally, we have previously reported that anaemia in these patients seems to be absolutely unresponsive to rHu EPO administration even after repeated dosage escalation (10). Transiliac bone biopsy revealed the typical histopathological existence of oxalosis that might cause extensive bone marrow fibrosis and subsequent displacement of the haematopoietic tissue(10–13). To carry out our experience to a greater extent, we have tested the reliability of bone marrow aspirate (BMA) so as to ascertain whether stone formers with ESRD are really affected or not by oxalosis. Furthermore, it might seem that our work is an illustrative example of the various diagnostic problems nephrologists from developing countries can face. So, the objectives of this study are first and foremost (1) to describe the clinical presentation in a cohort of urolithiasis induced ESRD patients presumably due to PH1 and (2) to extend knowledge about a useful diagnostic tool for PH1 in the developing countries.

METHODS

Subjects and data collection

This study focused on a cohort of 31 stone former patients identified in the south of Tunisia over a period of 18 years. Sixteen patients in this group had BMA because PH1 was suspected but not yet confirmed. Clinical and laboratory information were collected on chart review. Baseline characteristics such as sex, ethnic origin, family background of urolithiasis or PH1 and consanguinity were all recorded. Besides, clinical presentation and renal outcome (urolithiasis, nephrocalcinosis, dialysis, and kidney transplantation) were registered. Secondary forms of hyperoxaluria, the enteric, the dietary and the absorptive ones were excluded.

BMA procedure and analysis

Certainly, BMA procedure has been well described in standard textbooks, so we will not describe it in full detail (14). For the sake of the patient's comfort and confidence, an appropriate explanation of the procedure is essential; his consent was also obtained. Adequate local anaesthesia is likewise important in order to minimize pain. The patient was warned of the possibility of suction pain in advance and was also reassured that it would be brief. The BMA was performed to test its reliability in the diagnosis of oxalosis. Once dry, the films were carefully fixed in methanol and stained with a Romanowsky stain, May-Grüwald-Giemsa staining as an example. Indeed, BMA is considered as positive if in the photomicroscope study the oxalate crystal deposition is seen adjacent to hematopoietic cells and, when viewed under polarized light, shows the birefringent feature of oxalate crystals.

Although it is considered as an invasive procedure, transiliac BM biopsy has proved to be safe and free from serious complications besides pain but the operator's experience and skill are important in order to minimize morbidity and to obtain an adequate specimen (14). After being clinically indicated and accepted, the BM Bordier trephine biopsy was made by skilful and trained clinicians after an adequate local anesthesia. The specimen was immediately put in formalin fixative. Afterwards, fixation was embedded in resin or, more usually, decalcified and embedded in paraffin wax. Thin sections were cut and stained with haematoxylin, eosin and reticulin stain. In this case, a Giemsa stain is preferable. Actually, if deposition of polarizable oxalate crystals is visualised, it is considered as positive.

Statistical analysis

Results were expressed as mean±s.d for continuous variables. Diagnostic accuracy of this test, including sensitivity TP/(TP+TN),

specificity TN/(TN+FP), positive predictive value TP/(TP+FP) and negative predictive value TN/(FN+TN), were all calculated(15).

RESULTS

A thirty-one -cohort of unrelated patients was identified in the South of Tunisia over a period of 18 years. During that period, 2800 ESRD patients started renal replacement therapy and the disease incidence was 0.01. Most patients were offspring of consanguineous unions or descendants of married cousins of first-degree which was the most common pattern. In this cohort Seventeen were male and 14 were female. At the time of outbreak of renal symptoms, 12 patients were less than 15 years old, 5 patients were teenagers and 14 were adults. In diagnosis phase of PH1, ages ranged from 9 to 57 years (mean, 21.1±12.1 years). At this time, all patients had ESRD. In 4 patients, ESRD was associated with nephrocalcinosis whereas in 27 it was associated with recurrent nephrolithiasis. Diagnosis of PH1 was accomplished before starting dialysis in 10 patients, in the course of dialysis treatment in 18 and after renal transplantation in 3 due to of recurrence of the disease Table 1. No combined liver-kidney transplantation was performed. Twenty-one patients died on dialysis and one patient died after kidney transplantation. In 15 patients, diagnosis of oxalosis was based on clinical, family and/or biological investigation. Sixteen patients [mean age 27.2±12.2 years (range 11-57 years)] had BMA because PH1 was suspected but not yet confirmed. They safely underwent a BMA that was positive in 12 Figure 1 and negative in 4. Sensitivity (12/14) was 85%, specificity (2/2) was 100%, positive predictive value (12/12) was 100% and negative predictive value (2/4) was 50%. Furthermore, among the 4 patients whose BMA was negative, three had oxalosis deposits on their BM biopsy Figure 2. In addition, no evidence of serious complications was observed except for mild to moderate pain at the site of the bone biopsy in a few patients. Hence, this method is assumed to be a safe, valid and valuable diagnostic tool in oxalosis diagnosis.

Table 1. Patient characteristics

Male/female	17/14
Mean age at time of investigation (years)	27.2± 12.2
Mean age at time at occurrence of renal symptoms	21.1 ± 12.1
Pediatric onset of symptoms	12
Urolithiasis	27
Nephrocalcinosis	4
Renal insufficiency at the time of diagnosis	31
End-stage renal disease at time of diagnosis	18
Kidney transplantation	3
Death at last follow-up	22

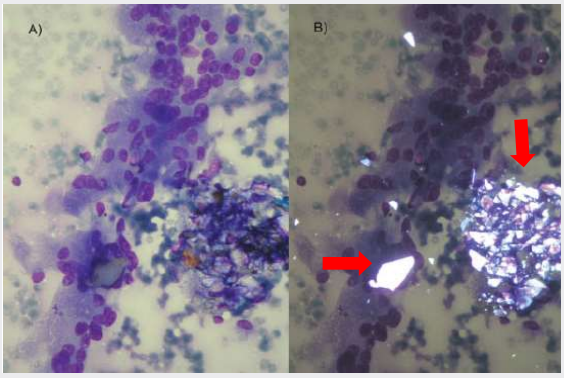

Figure 1. Oxalosis deposits on BMA (Red Arrow)

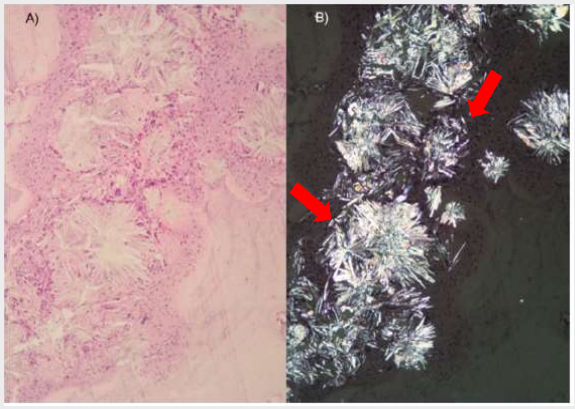

Figure 2. Oxalosis deposits on BM biopsy (Red Arrow)

DISCUSSION

BMA analysis for oxalate crystal deposition, assessment of pathological characteristics and clinical outcomes were performed in 16 patients from a Tunisian stone formers' cohort. The test was positive in 12 patients and negative in 4. Besides, Sensitivity (12/14) was 85%, specificity (2/2) was 100%, positive predictive value (12/12) was100% and negative predictive value (2/4) was 50%. Furthermore, among four BMA negative patients, three had oxalosis deposits in their BM biopsy. Literature review shows that until now nobody has provided such data within stone formers. Only in a few anecdotic case reports, bone marrow biopsy was performed not as a diagnostic tool of PH1 but as an investigation tool of treatment-resistant anemia (10–13) or of renal osteodystrophy diagnosis(16) among dialysis patients.

To the best of our knowledge, the diagnostic evaluation should be conducted in a stepwise manner. It should be primarily

based on clinical presentation, family history, urinary tract, plain X-ray, ultrasonography or any other imaging of the kidneys. Nephrocalcinosis is frequently found in infancy and early childhood. Later, urolithiasis without nephrocalcinosis is more often encountered (17–19). However, little attention has been paid to the stones' analysis as a possible diagnostic tool. Daudon et al. focused on the very peculiar stone morphology at the micrometer level, as demonstrated by scanning electron microscopic examination(20). Oxalates should be measured in 24 h urines even though normal urine value does not rule out the diagnosis. Once glomerular filtration rate (GFR) declines below 30 – 40 ml/min per 1.73m2 of the body surface area, urinary oxalate excretion decreases and becomes unreliable for the diagnosis (8). Definitive diagnosis of the disease could be based on liver biopsy and measurement of AGT activity in frozen tissue. Still considered to be the gold standard test, this analysis is restricted to a small number of centers worldwide. However, it is invasive and risky to some extent. Hence, the measurement of urinary glycolate and oxalate, also AGT activity seems to be limited to developed countries. Genetic testing is a crucial diagnostic tool for patients with PH to define the disease type (21). Molecular genetics has now reached a level of sensitivity and specificity that allows for a gene-based diagnosis. At least 146 mutations have been described, so far (22,23).

Actually, there is little association of mutation with ethnicity. The most noticeable exception is the Ile244Thr mutation and it is the most common mutation(24) that seems to have North African origins. It is called Maghrebian mutation and it may account for up to 91.6 % of AGXT mutations in northern African countries(25). Nevertheless, in an emergent country like Tunisia, dramatically marked by a high consanguinity level, the diagnosis of PH1 could be neither confirmed by determining AGT enzyme activity nor by searching Ile244Thr mutation since these sophisticated investigations were not applicable until the last decade. Indeed, genetic testing is available in some facilities of Tunisia (26,27), but unfortunately, due to unequal access to care, this test is not routinely performed when diagnostic is suspected. It is the same problem in the majority of third world countries.

A Tunisian medical team has proposed a limited mutation analysis as a useful first line investigation for primary hyperoxaluria, affording a low cost than whole gene sequencing (27).

If it is positive, the genetic testing can undoubtedly establish the diagnostic of oxalosis. Nevertheless, the disease's evolution and the systemic involvement might not be predictable because of phenotype genotype heterogeneity among others (28–30). These facts highlight the importance of having a specimen form the suffering patient for the sake of further accurate diagnosis such as bone marrow aspirate.

The disease is widespread in certain parts of the world including North Africa possibly due to consanguineous marriages, something rare in the western world (0.3 % in Europe and 0.7 % in North America) (31) and perhaps underreported worldwide. It is responsible for 17% of the ESRD in the Tunisian child (32). Compared to Western countries, in which the mortality rate ranges from 13% to 28% (29), PH1 is a life-threatening factor with an overall death rate of 70%; 22 out of 31 in our study.

Moreover, Tunisian prevalence is estimated to 5.5 per million population (pmp) (15) against an estimated prevalence that ranges from one to three pmp in Europe (33–35) and North America (36). Tunisian incidence is estimated to 0.23 pmp as compared to 0.12 and 0.15 pmp in France (33) and Holland (35), respectively. Higher rates are reported from inbred populations and this might be attributed to an elevated degree of consanguinity. Within the Tunisian and north African population, the frequency of unions between relatives was 30% in urban areas and 40% in rural areas(37). Marriages preferably take place within the same village, creating isolated communities that reside in small villages(37,38). It should be noted that other social determinants namely the population's migration might affect the trends of natural selection, anyhow.

In previous reported series from Tunisia, consanguinity ranged from 66% to 86 % (38–40), versus 11 % from Holland (35) and it even exceeded 76 % in patients of Muslim origins in France(41) Unfortunately, it seems that the disease is most frequently misdiagnosed or often diagnosed with delay (42). Surprisingly enough, some anecdotic cases of extra renal involvement such as stroke (43), paraplegia (44), cardiomyopathy (45,46), blurry vision and painful skin lesions (47) show primary hyperoxaluria.

Patients are oftentimes treated only in adult nephrology or in internal medicine departments(48). One third of the patients in some case series(36) and even more than two thirds in other series present only at ESRD(34). Some other patients, which is even worse, are diagnosed more or less accidentally on a biopsy performed after early kidney graft failure for suspicion of renal graft rejection insolently yielding disease recurrence that follows isolated renal transplantation (49–53) (and two additional personal cases). In Tunisia,

the graft is often provided by a living relative donor. Facing this avoidable catastrophe, the staff might admit a deep responsibility of the failure, which induced us to formulate a reliable approach to identify patients with PH1(54).

Liver transplantation completely corrects the enzyme defect. In Europe, with the poor results of isolated kidney transplantation reported two decades ago, combined or sequential liver-kidney transplantation has predominated thereafter (55,56).

The supportive treatment focuses on high fluid intake and crystallization inhibitors. Pyridoxine can reduce urinary oxalate excretion, but response is variable. Isolated kidney transplantation is reserved for pyridoxine sensitive patients only(57).

Recently an innovative class of medications such as RNA interference targeting the messenger RNA of glycolate oxidase showed encouraging results in reducing urinary oxalate excretion(58).

In fact, the inborn error of glyoxylate metabolism i.e PH1 causes excessive oxalate production from glyoxylate that accumulates behind the metabolic block. Indeed, glyoxalate does not transaminate to glycine but extends through the cytoplasm where it is converted into oxalate and glycolate Figure 3. Actually, in this hereditary metabolic disorder, the increasing production and excretion of poorly soluble oxalate leads to recurrent urolithiasis, nephrocalcinosis and frequent progression to ESRD. Vitamin B6 treatment can be provided for some patients with PH1(59) . In the Western world, most patients with renal stone disease present early so that primary diagnosis could be made and an adequate treatment could be launched (48). By contrast, in developing countries, the patients' late consultation and the physician's unawareness of the existence of PH1 frequently lead to a disastrous delay in diagnosis, which results in inadequate medical treatment and/or urological management with or without lithotripsy(39,40). Unfortunately, in the worst case, such as in the absence of an accurate diagnosis, cadaveric or regularly live related renal transplantation are performed and followed by a rapid recurrence of nephrocalcinosis. It leads to dialysis resume, transplanted kidney loss and disastrous iatrogenic medical complications of over immunosuppression caused by a misdiagnosis of the re-emergence of the disease wrongly handled as an acute rejection (49–53). Therefore, such situations should be carefully considered and a screening method for ruling out this multi systemic threatening disease is urgent (60).

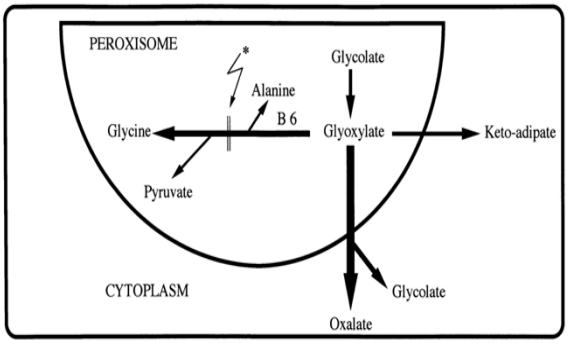

Figure 3. The metabolic defect in primary hyperoxaluria type 1. Deficiency of alanine: glyoxylate amino transferase (cofactor: pyroxidal phosphate) leads to high production of oxalate and glycolate.

CONCLUSION

Clinically, the rapid evolution to ESRD and the severe complications of oxalosis in PH1including the destruction of the transplanted kidney ensures an early diagnosis and treatment. Based on our positive clinical experience, we suggest that BMA could be performed for an early diagnosis of PH1. This might provide affected patients with a better chance to benefit from the early institution of adequate therapeutic management and might prevent the post-kidney transplantation recurrence of the disease, or substantially delay the consequences of misdiagnosing this devastating disease as well.

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