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Vascular Involvement in Primary Hyperoxalosis: An Evidence Based Sytematic Overview Over a Fifty Year Span

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Abstract

Background and Aims: Primary hyperoxaluria (PH) is a rare genetic disorder characterized by calcium oxalate nephrocalcinosis leading to renal failure. When renal function is impaired, plasma oxalate concentration increases and extra-renal oxalate deposition occurs. Vascular involvement includes vasculitis and ischemic related morbidity and death. The prevalence of vascular involvement is not known with only a few cases described in the literature. A systematic overview of the literature was performed to identify the demographics, clinical presentation and outcomes of such patients.

Methods: A computerized search of MEDLINE (Jan 1950 to May 30, 2007), EMBASE (Jan 1988 to May 2007) and CINAHL (Jan 1982 to May 30, 2007 identified twenty three cases of vascular involvement.

Results: The majority of those reported in the literature are young females (74%). Vascular deposition of oxalate crystals presents as skin vasculitis; limb or mesenteric ischemia or gangrene. Stroke is uncommon. The lower limbs are affected more than upper limbs followed by mesenteric vessels. Vasculitic skin manifestations occur in 52% of cases. Death occurred in 8 (38%) of cases (63% abdominal gangrene/sepsis; 37% cardiac).

Conclusions: Little information exists on vascular involvement in PH. Morbidity and mortality is high (death and limb loss occurring in 2/3 of patients). Awareness of the vascular presentation is thus important to allow a better understanding. Prospective reporting via a national or international registry on optimal management of vascular involvement in PH is needed.

Keywords: Nephrocalcinosis, Urolithiasis, Aminotransferase, Vasculitis, Vasculopathy, Skin Rash, Amputation, Gangrene, Hepatorenal Transplant.

Introduction

Primary hyperoxaluria (PH) is a rare genetic disorder characterized by calcium oxalate nephrolithiasis and nephrocalcinosis leading to renal failure, often with extrarenal oxalate deposition or systemic oxalosis. PH was first described by Lepoutre in 1925, but the first intra vitam diagnosis was in 1953 (1, 2). PH

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subtypes 1 and 2 are inherited as an autosomal recessive disorder.

PH type 1 (PH1), the most common type of PH, is caused by a deficiency of the peroxisomal liver enzyme alanine glycosylate aminotransferase (AGT) which normally converts glyoxylate to glycine (3-5). This defect results in an increased glyoxylate pool which leads to increased synthesis of poorly soluble oxalate (6). Oxalate overproduction coupled with renal excretion results in marked hyperoxaluria with nephrocalcinosis and recurrent urolithiasis. Most patients experience repeated episodes of urolithiasis in childhood, some develop renal failure as early as infancy, while others first present as adults with symptomatic urolithiasis (7).

PH type 2 (PH2), a less common form of PH, results from a deficiency in the cytosolic enzyme glyoxylate reductase. This enzyme is expressed in many cells including hepatocytes, renal parenchymal cells, fibroblasts, and lymphocytes. Glyoxylate reductase is responsible for the conversion of glyoxylate to glycolate. This defect similar to PH1, results in an increased glyoxylate pool which leads to increased synthesis of poorly soluble oxalate (8).

Non type 1, non type 2 PH is currently used to describe a heterogeneous group of not other wise six articles were identified. Seventeen articles were deemed relevant (i.e. they have vascular involvement directly due to primary hyperoxaluria). Twenty three patients with primary hyperoxaluria and vascular involved were identified. The bibliographies of all relevant articles were also searched for new cases.

End points

The end points include any form of vasculopathy or vasculitis including any vascular bed as well as skin vasculitis, ulcerations, limb gangrene and or amputation, death and stroke. Radiological, histopathological biopsy or post surgical tissue diagnoses were considered confirmatory.specified variants of PH, extrarenal deposition of oxalate occurs in bone, retina, arterial media, nerves, skin, and myocardium (8-15). Symptoms of systemic oxalosis in patients with PH1 are often ameliorated or corrected with combined hepato-renal transplant, which is considered curative therapy. Vascular manifestations can result in vasculitis or significant ischemic related morbidity and death. The true prevalence of vascular involvement is not known with few cases in the literature. The aim of this paper is to perform a systematic overview of all published reports on vascular manifestations of PH and to describe the demographics, clinical presentation, diagnosis, treatment and outcomes of this group of patients.

Materials and Methods

A computerized search of OVID MEDLINE (Jan 1950 to May 30, 2007), EMBASE (Jan 1988 to May 2007) and CINHAL (Jan 1982 to May 30, 2007) was performed. The following search terms were used to identify English language studies: ‘Primary hyperoxaluria vasculitis’; ‘primary hyperoxalosis and vasculitis’; ‘Primary hyperoxaluria, vascular disease’; Primary hyperoxaluria, vascular involvement. Sixty

Statistical analysis

Age and gender were expressed as means and standard deviations Groups by gender and organ involved were compared by the absolute number of cases (n) and percentages (%) of the total reported cases included in the study.

Results

Twenty three patients with vascular complications of systemic oxalosis were identified. Clinical information is summarized in table 1 and distribution of the vascular lesions in table 2. Of the twenty three patients, mean age was 34±13, 17 (74%) were female.

Table 1. Studies of vascular involvement including demographics, clinical presentation and outcomes in PH

Case	Age/ Sex	Presentation	Diagnostic Tool	Treatment	Vessels	Outcome
Christopher J/2004	25 F	Bilateral foot pain + skin discoloration	CT Angio	Distal to popliteals/ superior mesenteric art	Cyclophosphamide + prednisone + CCB	Death of cardiac complications
Vincent M/2002	40 F	S/C painful nodules on left arm & bilateral lower limbs	Skin biopsy	?	?	prepared for transplant
Herrmann G/ 2004	49 F	dermal plaques on both thighs	Skin biopsy	?	UV A1 therapy+ oral Oxf	slight improvement
Somach/1995	38 F	painful eruptions on lower limbs	Skin biopsy	?	?	death of sepsis
Shih /2000	39F	purpura on both upper and lower limbs	Liver biopsy	?	fentanyl patches + mupirocin oint	toes amputation
Jonshon J /2000	49 F	pain in both feet	Kidney biopsy	calf vesels /small intestinal	prostsacyclin infusion	death of acute abdomen
O Reilly/2001	25 F	necrotic lesions on the extremities	CT Angio + skin biopsy	extremity vessels	Cyclophosphamide + prednisone	death of cardiac complications
Damme- /	16 F	claudication + skin discoloration	Kidney biopsy	femoral & popliteal	Na nitroprus-side + excess Mg	improved, disappeared after renal transplant
Arbus- /1974	10 F	gangrene in all extremities	CT Angio & X-Rays	arteries of legs	epidural anesthesia & hyperbaric O2	Death
Blackburn/1975	18 F	gangrene	CT Angio	Femoral + hypogas tric	?	Death
Boquist et al/1973	44 M	ischemic changes in arms & legs	?	?	?	Death
Vanrenter-ghem/1984	54 M	progressive vascu-lar lesions	?	?	?	amputation of both legs and one arm
Riksen /2002	51 M	progressive claudication	Kidney biopsy	distal art of LL	IV steroids	?
Marc F/1986	27 M	ischemic changes of left LL	CT Angio	LL vessels	?	below knee amputation
Candido/2004	18 F	paresthesia & cold lower limbs	Echo- Doppler	right ant tibial, pulmo-nary, & cerebral micro- cir-culation	vasodilators	partial response to treatment
Suneet /1999	54 F	livedo reticularis	Liver biopsy	?	Steroids	symptoms improved
Bastani/1999	23 F	livedo reticularis	Skin biopsy	?	?	improved after liver transplant

continued of Table 1.

Melissa/2004	30 F	livedo reticularis + ulcers on legs	Renal + skin biopsy	?	enzymatic debridments	death of cardiac complications
John /1997	22 F	livedo reticularis in lower limbs	Skin biopsy + echo	?	?	improvement after 2nd renal transplant
Jansen /1974	27 F	spasms of hands + facial paresthesias	CT Angio & skin biopsy	left internal & external carotids	?	right leg amputation
Jansen /1974	42 F	progressive renal function impairment	Renal, skin, arterial biopsy	?	?	?
Freiberg /1993	38 M	worsening digital pain	hand X-ray	?	CCB & digital sympathec-tomy	Finger and toes amputation
Freiberg /1993	35 M	muscle weakness & white tissue deposits on both hands	?	?	?	?
Freiberg /1993	35 M	muscle weakness & white tissue de-posits on both hands	?	?	?	?

PH, primary hyperoxaluria; **CT**, Computerized Tomography; **?**, no data available

Diagnostic modalities

All twenty three cases reported clinical manifestations suggestive of vascular involvement due to PH. More than half of the reported cases 14 (61%) were diagnosed by biopsy (skin-9=39%, kidney-5=22%, liver-2=9%, arterial-1=4%). It should be noted that patients with calciphylaxis can present with livedo reticularis, therefore skin biopsy is necessary toa skin rash, 12 (52%) with livedo (11 with livedo reticularis and only one case with livedo racemosa) and 4 (17%) with skin ulceration, Vasculitis in association with limb ischemia occurred in all 23 cases (100%).

Ischemic Limb

Limb ischemia was more common in the lower limbs affecting 21 (91%) patients. Single limb vasculitis occurred in 1 (4%), 2 limb ischemia in 12 (52%), 3 limb ischemia in 3(13%). Seven (30%) patients had both upper and lower limb involvement.

Bowel Ischemia

The third commonest manifestation of vasculitis presented with bowel ischemia in 3 (13%) and frank

Table 2. Patient demographics, clinical presentation and outcomes

	No. (%) of patients
AGE, range (mean ± SD)	10-54 (34 ± 13) years
GENDER	
Male	6 (26)
Female	17 (74)
CLINICAL PRESENTATION	
Livedo	12 (52)
gangrene	3 (13)
Cutaneous ulcers?	4 (17)
Abdominal pain	2 (9)
stroke	2 (9)
Limb: Upper vs lower	9 (39) vs 21 (91)
Mesenteric vessels	3 (13)
Carotids	1 (4)
Cerebral	1 (4)
VASCULAR STUDIES	
Biopsy	14 (61)
CT angiography	6 (26)
Ultrasound	2 (9)
MRA	1 (4)

gangrene was present in 3 (13%). Overall mortality in this group was 8 (38%). In the 3 (13) patients with bowel ischemia mortality was 100%.

Other vasculopathy

There was only one case (4%) each of carotid arteryand one case (4%) intracerebral artery involvement.

Management

Medical management of these patients included hyperbaric oxygen and immunosuppressive therapy with cyclophosphamide and steroids in 4 (17%) while vasodilators such as calcium channel blockers and magnesium were used in 5 (22%) and UV A1 therapy in one case (4%). Significant improvement in vascular manifestations was reported in 3 (13%) cases that underwent hepatorenal transplant. In the cohort of limb ischemia amputations were necessary in 6/21 (29%) patients. Bowel resection was done in one patient who died two days later.

Discussion

The primary hyperoxalurias are a group of rare autosomal recessive metabolic disorders that lead to an accumulation of oxalate in the body (16). Early in the course of the disease, calcium oxalate deposits are confined to the kidneys where oxalate clearance usually takes place. Once significant renal insufficiency develops, the kidneys are no longer able to excrete the large excess of oxalate produced.

On histologic examination of the blood vessels in these reports, the deposits were limited to the vessel wall, with arterial and arteriolar involvement being more common than venous involvement in most of the cases (17). Crystal deposition in the tunica media of arteries leads to subintimal fibrosis followed by arteriolar occlusion and occasional thrombosis (16). The vascular obliteration accounts for livedo reticularis and ischemia to tissues (16). Livedo is the commonest presentation of vascular involvement in patients with primary hyperoxaluria 12 (52%). Deposits of calcium oxalate in the superficial arterioles leads to cutaneous ischemia subsequently leading to the livedoid pattern (16). Thus the development of livedo reticularis in a patient on dialysis should raise the suspicion of the possibility that PH may be cause of end stage renal disease (15).

All cases included in our study showed signs of limb ischemia with the lower limbs being affected in the majority of 21 (91%) and 7 (30%) had all upper and lower limbs involvement. Only one case (4%) showed single limb ischemia. Three cases (13%) had mesenteric vessels affected with 100% mortality.

Treatment was mentioned in about half the reports. Five (22%) were treated with vasodilators such as calcium channel blockers, magnesium, and Na nitroprusside. Four of them (17%) were given immunosuppressives such as cyclophosphamide and steroids on the basis that this was a vasculitis with an inflammatory reponse. Furthermore UV A1 therapy was used in a single case as was hyperbaric O2. No single treatment used showed significant improvement in the patient's symptoms. Three cases reported significant improvement in the vascular manifestations after combined hepato-renal transplant (14), one patient developed vascular involvement after hepato-renal transplantation (9, 14).

Taking into consideration the age at which some of the cases included in our study were reported, the mortality rate was high at 38% (8 cases). Three patients died of cardiac complications and three of sepsis. Cause of death was unspecified in the 2 remaining cases. Of the twenty three cases three patients also had retinal oxalate deposition, three cases showed bone deposits, and one patient had both pancreatic and gall bladder involvement from primary hyperoxaluria.

Conclusions

Little information exists on vascular involvement PH. Among published reports whose disease progressed to renal failure, and who developed vascular oxalosis, morbidity and mortality appears high (death and limb loss occurring in 2/3 of patients). The majority are young females (74%). Vascular deposition of oxalate crystals presents as skin vasculitis, cutaneous ulcers, limb or mesenteric ischemia or gangrene. The lower limbs are affected more frequently than the upper limbs followed by the mesenteric vessels. Vasculitic skin manifestations occur in 52% of cases. Systemic oxalosis in patients with vascular involvement is often fatal (death in 38%). The most sensitive tools for assessing vascular involvement are the clinical examination, non-contrast CT imaging and computerized tomographic angiography in addition to skin biopsy. Although several types of treatments were attempted, none was of clear benefit. The optimal management appears to be early recognition of the disease, followed by avoidance of high serum oxalate levels by frequent dialysis and early curative dual organ hepato-renal transplantation. In cases where serum oxalate levels are high or vascular involvement established at the time of transplantation, then post transplant dialysis to remove as much of the serum oxalate as possible may be beneficial. Prospective reporting on vascular manifestations via a national/ international registry is important to allow a better understanding of the frequency, complications and optimal management of vascular involvement in the primary hyperoxalurias.

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Conflict of Interest

None declared.

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