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Original Article

Outcomes of hydralazine induced renal vasculitis

Homa Timlin[1], Jason E. Liebowitz[1], Khusleen Jaggi[2], Duvuru Geetha[1,2]

Abstract

Objective: Hydralazine has been implicated as an etiologic agent for lupus-like syndrome and vasculitis. Hydralazine-induced vasculitis frequently affects the kidney, but the long-term renal outcomes in these patients have not yet been studied.

Methods: Patients who had a diagnosis of ANCA-associated vasculitis (AAV) and were on hydralazine at the time of AAV diagnosis were included in this retrospective cohort study. Clinical and laboratory data were obtained from the review of medical records.

Results: Seven patients met the criteria for hydralazine-induced AAV. Five patients (71%) were African-American and four (57%) were female. The median age was 69 years at the time of diagnosis. All patients had renal involvement with two of them showing lung involvement as well. All patients had positive MPO antibody and one patient had positive PR3 antibody. ANA was positive in all patients, and three of seven patients had positive anti-histone antibody. All of them were treated with immunosuppression and withdrawal of hydralazine. Three patients reached end-stage renal disease. The median follow-up time was 13 months.

Conclusion: Renal involvement in hydralazine-induced AAV was universal and can be associated with a poor renal outcome despite immunosuppressive therapy.

Keywords: Hydralazine, ANCA associated vasculitis, antinuclear antibody, end-stage renal disease

Introduction

Hydralazine hydrochloride is an FDA-approved medication for the treatment of essential hypertension. Hydralazine is also recommended by the American Heart Association (AHA) for the treatment of congestive heart failure in African-Americans (1). Among many adverse effects, the auto-immunogenic capability of hydralazine has been shown through its ability to induce lupus and vasculitis (2-4). Hydralazine-induced lupus was first described in 1953. Hydralazine-induced lupus differs from idiopathic lupus both clinically and serologically. Hydralazine-induced lupus rarely involves the kidneys or nervous system, and serologically, while all patients are positive for ANA, they do not have positive double-stranded DNA or hypocomplementemia. In contrast to hydralazine-induced lupus, hydralazine-induced vasculitis can be severe with frequent involvement of the kidneys. Hydralazine-induced vasculitis involving the skin was first reported in 1980, and vasculitis involving the kidneys was first suspected in 1981 (5, 6). Cases of rapidly progressive glomerulonephritis were reported in 1983, and subsequently, ANCA positivity was demonstrated in some of these cases (7, 8). While the cessation of hydralazine therapy helps non-organ-threatening manifestations of hydralazine-induced vasculitis, the renal outcomes of these patients are not clear. We conducted this single-center, retrospective study to identify patients with hydralazine-induced renal vasculitis and describe their outcomes.

Methods

Study population

Patients for this single center study were identified from a clinic database for the study period 2014 to 2016. Subjects who met the 2012 Chapel Hill Classification criteria for granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) (9) and were on hydralazine therapy prior to diagnosis of AAV were identified as having hydralazine-induced vasculitis. The Office of Human Subjects Research and Institutional Review Board approved this study protocol as an exempt study.

Acquisition of clinical and laboratory data

Patient demographics, clinical features, dose and duration of hydralazine exposure, and details of immunosuppressive therapy were abstracted retrospectively from the electronic medical records. Peak serum cre-

ORCID IDs of the authors:
H.T. 0000-0002-4320-8106;
J.E.L. 0000-0002-9759-1681;
K.J. 0000-0001-7470-2337;
D.G. 0000-0001-8353-5542.

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[1] Department of Rheumatology, Johns Hopkins Bayview Medical Center, Baltimore, USA
[2] Department of Nephrology, Johns Hopkins Bayview Medical Center, Baltimore, USA

Address for Correspondence: Duvuru Geetha, Department of Nephrology, Johns Hopkins Bayview Medical Center, Baltimore, USA

E-mail: gduvura@jhmi.edu

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atinine at the time of diagnosis and serology including ANA, ANCA, anti-histone antibody, and serum complement levels were recorded. ANCA testing was done by standard indirect immunofluorescent assay on ethanol-fixed neutrophils for cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA). PR3 and myeloperoxidase (MPO) testing were done by direct enzyme-linked immunosorbent assay (ELISA) with commercially available kits at the local laboratory.

Study definitions

Renal function was estimated using the four-variable modification of diet in renal disease (MDRD) formula for estimated GFR (e-GFR) (10). Renal involvement was defined by biopsy-proven glomerulonephritis or clinically by increase in serum creatinine with hematuria and proteinuria. Proteinuria was defined by urine protein:creatinine ratio of >0.2. Other organ involvement such as lung, heart, and skin was defined by imaging and a diagnostic biopsy. Remission was defined by a Birmingham Vasculitis Activity Score of zero.

All descriptive data are presented as median with range or mean with standard deviation.

Results

Seven patients met the criteria for hydralazine-induced vasculitis. The median age was 69 years (range, 42-86 years). Five patients were older than 65 years. Five were African-American, and the remainder were Caucasian. All the patients were exposed to hydralazine, but the majority of these patients were exposed for less than 12 months (57%). All patients had renal involvement, two had lung involvement, and a single patient had skin and heart involvement in addition to the kidney. The mean e-GFR was 20 ml/min/m^2 (SD, 15), and the median e-GFR at presentation was 12 ml/min/m^2 (range, 9-51). Three patients required dialysis at presentation (Table 1). The median follow-up time was 13 months (range, 5-18 months).

Table 1. Demographics and clinical presentation

Subject number	Age	Gender	Race	Hydralazine dose	Hydralazine exposure duration (greater than or less than 12 months)
1	86	M	W	100 mg tid	Less than 12 months
2	50	M	AA	100 mg tid	More than 12 months
3	42	F	AA	50 mg bid	More than 12 months
4	74	F	W	10 mg qid	Less than 12 months
5	69	F	AA	50 mg bid	Less than 12 months
6	65	F	AA	100 mg tid	Less than 12 months
7	73	M	AA	100 mg tid	More than 12 months

M: male; F: female; W: white; AA: African-American; bid: twice daily; tid: three times daily; qid: four times daily

ANA and p-ANCA were positive in all patients. Six patients were positive for MPO ANCA with titers greater than 320 and one was positive for both PR3 ANCA and MPO ANCA. Three of five patients tested for anti-histone antibody were positive. Serum complement was measured in six patients but only one had low levels (Table 2). Six patients underwent a renal biopsy. One had necrotizing vasculitis with no evidence of glomerulonephritis (GN), one had necrotizing GN with electron-dense deposits on electron microscopy (EM) and the remaining 4 had pauci-immune necrotizing GN.

Hydralazine therapy was stopped in all patients. Two patients with pulmonary renal syndrome were treated with plasma exchange. All seven patients received glucocorticoids. Six patients received additional immunosuppressive therapy with cyclophosphamide (n=3) and rituximab (n=4). One patient was switched from cyclophosphamide to rituximab due to bone marrow suppression (Table 3). Remission was achieved in all patients. Of the three patients who were dialysis-dependent on presentation, one had recovered sufficient renal function to discontinue dialysis and the remaining two patients reached end-stage renal disease. In addition to these two patients, the single patient treated only with glucocorticoids progressed to end-stage renal disease. None of the patients received maintenance immunosuppression. No disease relapses have been observed during the follow-up period.

Discussion

This single-center, retrospective study of hydralazine-induced vasculitis demonstrates that organ involvement is common and often severe at presentation. Withdrawal of hydralazine

Table 2. Clinical and serologic features

Subject number	Organs involved	Biopsy	Serum creatinine /GFR at entry (mL/min/m^2)	Dialysis dependent at entry	PR3 ANCA	MPO ANCA	ANA	Anti-histone	Low serum complement
1	K, C, S	K: necrotizing vasculitis C: myocarditis S: leukocytoclastic vasculitis	2.1/30	N	N	Y	Y	N	N
2	K	K: necrotizing pauci-immune GN and diabetic nephropathy	5.1/12	N	N	Y	Y	Y	N
3	K, L	K: no renal biopsy L: alveolar hemorrhage	1.17/51	N	N	Y	Y	ND	ND
4	K	K: necrotizing and crescentic GN	2.3/20	N	N	Y	Y	N	N
5	K	K: necrotizing and crescentic GN	8.9/9	Y	N	Y	Y	Y	Y
6	K	K: necrotizing and crescentic GN	6.5/11	Y	Y	Y	Y	Y	N
7	K, L	K: necrotizing and crescentic GN L: lung nodules	7.7/9	Y	N	Y	Y	ND	N

K: kidney; C: cardiac; S: skin; L: lung; GFR: glomerular filtration rate; ND: no data

Table 3. Treatments and outcome

Subject number	Steroid	CYC	RTX	MMF	PLEX	Serum creatinine (GFR) at 3 months	ESRD
1	Y	Y	N	N	N	1.6/40	N
2	Y	N	N	N	N	ESRD	Y
3	Y	N	Y	N	N	1.07 (64)	N
4	Y	N	Y	N	N	2.14 (26)	N
5	Y	Y	N	N	Y	ESRD	Y
6	Y	N	Y	N	N	ESRD	Y
7	Y	Y	Y	N	Y	4.3 (16)	N

CYC: cyclophosphamide; RTX: rituximab; MMF: mycophenolate mofetil; PLEX: plasmapheresis; ESRD: end-stage renal disease

and immunosuppressive drug therapy are effective in inducing disease remission, but the renal outcomes of these patients remain poor.

Reports of rapidly progressive renal failure in patients taking hydralazine were initially reported in the 1980s (4, 7, 11). The association of ANCA with glomerulonephritis was first described in 1991; in this report, nine patients with hydralazine-induced glomerulonephritis were found to have antibodies to myeloperoxidase and elastase (8). Since this initial report, several case reports and case series have described vasculitis in patients taking hydralazine. A review in 2009 reported 68 cases of hydralazine-induced vasculitis, and in this case series, the mean age of patients with hydralazine-induced vasculitis was 64 years, the majority of patients were Caucasian, and the mean duration of exposure to hydralazine was 4.7 years. Organ involvement was common, with renal involvement being the most common, followed by skin, joint, lungs, upper airway, eyes, and nerves (6). All patients had antibodies to MPO, ANA was positive in 96% of patients, and hypocomplementemia was noted in 44% patients. In our study, the mean age of patients was similar (69 years), and all patients had positive MPO antibody and positive ANA, but, in contrast to the review noted above, a greater proportion of patients were African-American, four of the seven patients were exposed to hydralazine for less than 12 months, and hypocomplementemia was rare. Similar to the review, our patients had predominantly renal involvement and one patient had cardiac involvement as well.

The MPO ANCA in patients with hydralazine-induced vasculitis is often in high titer, and patients often have antibodies directed to other antigens for perinuclear, elastase, and lactoferrin (8, 12, 13). The mechanism by which hydralazine induces MPO antibodies and vasculitis is not clear. It is hypothesized that hydralazine is metabolized by myeloperoxidase released from activated neutrophils to form reactive intermediate metabolites, which can act as hapten for MPO and result in formation of anti-MPO antibody (14). This in turn causes neutrophil respiratory burst that releases histone DNA complexes into extracellular tissue, known as neutrophil extracellular traps (NETs), which causes endothelial injury (14). The second mechanism by which hydralazine can cause vasculitis relates to the function of hydralazine as DNA methylation inhibitor. This causes increased expression of neutrophil antigens by reversal of epigenetic silencing of PR3 and MPO (15). Finally, hydralazine acetylation differs in fast acetylators versus slow acetylators, and break in tolerance is more likely in slow acetylators (16).

Treatment of hydralazine-induced vasculitis requires withdrawal of hydralazine in all patients and, frequently, also involves immunosuppressive therapy. The renal outcomes in patients with hydralazine induced vasculitis have been variable. For example, one series of four patients on chronic hydralazine who developed pauci-immune glomerulonephritis reported that the creatinine for all patients return to baseline or close to baseline within 6 months of follow-up (17). In contrast, in a case series of 17 patients with suspected hydralazine-induced nephritis in which minimum follow-up was 6 months, five patients required dialysis within 2 weeks to 6 years of stopping hydralazine and one patient died of uremia (18). In our series, three of seven patients reached end-stage renal disease despite immunosuppressive therapy. This includes one patient treated with corticosteroid, cyclophosphamide, and plasma exchange and another patient treated with corticosteroid and rituximab; it is worth noting that the GFR values for these patients were 9 and 11, respectively, at time of entry. Of the remaining four patients, only one patient reached a GFR > 40 at 3 months of follow-up, indicating generally poor renal outcomes for the majority of the patients in this series.

Our study is limited by small sample size, short follow-up time, and limitations inherent in a retrospective study. After hospital discharge, their local physicians followed majority of the patients, and hence we are unable to assess long-term outcomes. In addition, our patients were not tested for antibodies to other p-ANCA antigens such as elastase and lactoferrin. Despite these limitations, this study provides insight into the renal outcomes of patients with hydralazine-induced ANCA vasculitis in the context of several different immunosuppressive treatment regimens.

This study also helps to characterize the phenotype of patients in which hydralazine-induced ANCA vasculitis should be suspected. Indeed, our study indicates that consideration for hydralazine-induced ANCA vasculitis should be higher for patients who are African-American, if they have positive MPO ANCA antibody at a high titer, and if they have positive ANA. From the other studies cited in this article, antibodies to elastase and lactoferrin are also common in hydralazine-induced ANCA vasculitis and hypocomplementemia can be seen, although it was rare in our study population. Treatment for hydralazine-induced ANCA vasculitis includes stopping hydralazine, which should be avoided in perpetuity and listed as a drug allergy, as well as timely initiation of immunosuppressive therapy in patients with severe organ involvement. The renal outcomes can be poor despite immunosuppressive therapy, and therefore, a high index of suspicion and early diagnosis of hydralazine-induced vasculitis is crucial. Further research is needed to clarify the pathogenesis of hydralazine-induced vasculitis and to develop efficient biomarkers for diagnosis and help predict individuals at risk for the disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study. The study was an exempt IRB.

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