RESEARCH LETTERS

Nephrogenic Systemic Fibrosis and Diabetes Mellitus

Over the past decade, specialists in all areas of medicine have become increasingly aware of and interested in nephrogenic systemic fibrosis (NSF), yet much of this devastating disease’s pathogenesis remains a mystery. Many risk factors have been implicated, including liver disease, erythropoietin, proinflammatory and hypercoagulable conditions, dialysis, and gadolinium exposure. Diabetes mellitus (DM) and renal failure are both associated with fibrosing disorders. While a strong association exists between kidney disease and NSF, diabetes has never before been proposed as a risk factor. The most common cause of renal failure in the United States is DM. Seven percent of the population has diabetes, and every third patient with DM develops nephropathy, accounting for about 45% of end-stage renal disease (ESRD). Herein, we review 295 cases of NSF to determine if diabetes could be a risk factor for NSF development.

Methods. To examine the prevalence of DM among patients with NSF, a PubMed literature search was performed for articles published between 1997 and September 2011 containing the terms nephrogenic systemic fibrosis and nephrogenic fibrosing dermopathy. Resulting articles from any country in any clinical setting that provided clinical descriptions and data for each patient with histologic evidence of NSF were analyzed. Articles containing known previously reported cases were excluded. A total of 81 articles describing 295 patients were included in our final analysis (eReferences available at http://www.archdermatol.com). Each patient’s age, sex, gadolinium exposure, dialysis history, cause of renal failure, comorbidities, and diagnosis of DM were tabulated. Prevalence rates of diabetes and other causes of renal disease were calculated and compared with current data from the United States Renal Data System (USRDS) using a χ² goodness-of-fit test.

Results. Table 1 summarizes demographic data. All patients had some degree of renal failure. Most had been undergoing hemodialysis and/or peritoneal dialysis, although 12 patients (4.1%) were reported to never have had dialysis. Most had chronic renal disease or ESRD, although 26 patients (8.8%) had acute kidney injury. Fifty-seven patients were reported to have diabetes (19.3%). All but 1 were undergoing dialysis (or dialysis information was not provided). The mean (SD) age of the diabetic group was 57.5 (12.7) years; 49% were men. The mean (SD) age of the nondiabetic group was 47.6 (16.4) years. Of all 295 patients, 54% had exposure to gadolinium; 41% had unknown or unrecorded gadolinium exposure histories; and 5% had never been exposed to gadolinium. Of the diabetic patients, 45.6% had exposure to gadolinium, 50.9% had unknown or unrecorded exposure histories, and 3.5% had no exposure. Of the 12 patients who never had dialysis, all had either been exposed to gadolinium or had unknown or unrecorded exposure histories.

Table 2 lists the 229 cases of ESRD where a primary cause was identified. The prevalence of diabetes among these patients with NSF (18.8%) was much lower than the expected USRDS rate of DM in all patients with ESRD (45%). Patients with NSF also had a higher rate of glomerulonephritis than expected, even when only “true” glomerulonephritides were analyzed (excluding focal segmental glomerulosclerosis, membranous and human immunodeficiency virus nephropathies, nephrotic syndrome, and minimal change disease). Results of a χ² goodness-of-fit test (χ²=424.69) (P<1.0×10⁻¹⁰) indicate statistical significance in this difference in ESRD cause distribution among patients with NSF patients compared with expected USRDS rates.

Besides renal disease, the most prevalent comorbidities among all patients are listed in Table 3.

Comment. Prevalence rates of renal failure and gadolinium exposure among patients with NSF in this analysis are consistent with those found in other studies.

Table 1. Known Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Age Range, y (n = 236)</th>
<th>Sex (n = 269)</th>
<th>Renal Disease</th>
<th>Dialysis History</th>
<th>Gadolinium Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-83</td>
<td>139 M, 130 F</td>
<td>269 (54) Chronic; 26 (3) acute</td>
<td>270 (47) HD or PD or both; 13 (9) unknown or unrecorded dialysis status; 12 (1) never had dialysis</td>
<td>160 (26) Yes; 120 (29) unknown or unrecorded; 15 (2) no</td>
</tr>
</tbody>
</table>

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis.

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Our data also indicate an underrepresentation of diabetes mellitus among patients with NSF. To our knowledge, this is the first report of a possible protective quality of diabetes against NSF. Glycosylated tissue may have a low affinity for gadolinium. Pharmacologic treatments for DM (insulin or oral hypoglycemics) may confer protection. Diabetic patients often have comorbid conditions that may contribute to or confound this finding. Though rarely described in NSF reports, variables such as cause, type, duration, and glycemic control of diabetes may offer clues. Our data also indicate an underrepresentation of hypertension and an overrepresentation of glomerulonephritis, urologic disease, and cystic kidney disease. Whether this reflects infectious, autoimmune, other specific inflammatory changes, or an unidentified confounder is beyond the scope of this analysis. Further research may elucidate the reason for this relationship between diabetes and NSF and aid in developing new treatments.

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Author Contributions: Drs Schleichert and Gaspari had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Schleichert, Seliger, and Gaspari. Acquisition of data: Schleichert and Gaspari. Analysis and interpretation of data: Schleichert, Zhan, and Gaspari. Drafting of the manuscript: Schleichert and Gaspari. Critical revision of the manuscript for important intellectual content: Schleichert, Seliger, Zhan, and...
A Randomized, Double-blind, Placebo-Controlled Proof of Concept Trial of Topical Cidofovir, 1% and 3%, for the Prevention of Beard Hair Growth in Men

Unwanted facial hair, hirsutism, and pseudofolliculitis barbae occur commonly, and billions of dollars are spent annually on hair removal products.1,2 Eflornithine, the only prescription topical agent approved in the United States for female facial hirsutism, has only a 32% success rate and has not been evaluated in men.3 Therefore, additional topical treatments effective in preventing hair growth are needed. The antiviral agent cidofovir has been reported to induce alopecia as was previously reported when topical cidofovir was applied to the face in healthy men.1 Therefore, additional topical treatments effective in preventing hair growth in healthy men are needed.

Methods. Eligible participants were men who shaved daily and had beards scoring 4 (dense) or 5 (very dense) on the physician general assessment (PGA) of hair density.1 Subjects were excluded if they used any medication affecting hair growth or had a history of alopecia areata. The study was approved by the institutional review board and registered at ClinicalTrials.gov (NCT00948506).

Subjects were randomized as to which side of the face received cidofovir or placebo and to either the 1% or 3% concentration. Cidofovir and placebo were applied once daily after shaving to a circular area (2.5-cm diameter) within the beard in a split-face design. Templates delineating the treatment area were used in drug application and evaluation.4 Treatment duration was increased from 6 to 8 weeks following an interim analysis of the first 5 subjects. Subjects were evaluated every 2 weeks during treatment; those receiving 6-week treatment were evaluated post treatment at weeks 8 and 10, while those receiving 8-week treatment were seen at weeks 10 and 12 only if they had a PGA change or unresolved adverse event at week 8. Subjects did not shave for 48 hours before visits to grow visible hair for assessment.

At each visit, the investigator performed a PGA and photographed the treatment areas. The number of hairs within the treatment area in each photograph were counted as previously described.5 Laboratory test results, including for renal and liver function, were assessed at baseline and every 2 to 4 weeks.

The primary outcome was response to treatment, which was defined as a PGA score of 2 (sparse) or lower at the end of treatment. We compared response rates and hair count changes between cidofovir and placebo sites in both intention-to-treat and as-treated populations. Data were analyzed using Stata IC, version 10 (StataCorp LP).

Results. Of 39 subjects screened, 20 were enrolled. Seventy percent of subjects were white (n=14), 15% black (n=3), and 15% Asian (n=3). The median age of subjects was 32 years (interquartile range, 26-42 years). Four subjects withdrew during treatment owing to scheduling conflicts and health problems unrelated to the study. Sixteen subjects (8 each in the 1% and 3% groups) completed treatment, and 11 subjects followed up post treatment. Baseline PGA scores and hair counts did not differ significantly between the active and placebo groups or between the 1% and 3% groups (Table). All subjects had normal baseline blood urea nitrogen and creatinine levels.

We observed a 5% (95% confidence interval 0.1%-24.9%) response rate in the cidofovir and placebo groups (Table). Hair count changes did not differ significantly between the cidofovir and placebo sites. However, we observed a negative trend in hair counts within the 3% group compared with placebo (median difference in hair count changes [ΔΔ] =-73) (P=.08).

Twelve subjects experienced 24 adverse events, the most common being upper respiratory infection (20%; [n=4]), headache (15%; [n=3]), and erythema and/or hyperpigmentation (15%; [n=3]), or pruritus of the treatment area (10%; [n=2]). However, all local skin reactions were mild and independent, did not require stopping application of the drug, and resolved with little or no intervention by 8 weeks after treatment cessation. No significant changes in laboratory values were observed.

Comment. The negative trend in hair count with use of cidofovir, 3%, suggests a dose-response relationship and that the 3% concentration may be promising for preventing hair growth. We did not observe induction of total alopecia as was previously reported when topical cidofovir was applied to virally infected skin of immunocompromised patients.3 Treatment dose and duration may have been insufficient to trigger cidofovir's effect in normal skin. Nevertheless, topical cidofovir was well tolerated and showed an incidence of local skin reactions similar to that of eflornithine.1

Limitations of this trial include the low statistical power of a small study. The use of templates to localize the treatment area may have introduced variability in drug application or evaluation. Finally, preventing facial hair growth in men may be a high-efficacy bar relative to preventing facial hair growth in women; cidofovir likely needs to reach the rapidly proliferating bulb matrix cells in the deepest portion of the follicle.