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Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome

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ABSTRACT

Background: Posterior reversible encephalopathy syndrome (PRES) is a variable cerebrovascular syndrome associated with hypertension and autoregulatory failure. Steroids have been reported to both precipitate and treat PRES. We sought to determine the prevalence of steroid therapy at the time of PRES and to assess the relationship between steroid therapy and extent of vasogenic edema.

Methods: We performed a retrospective review of radiology reports between 2008 and 2014 from two academic medical centers to identify cases of PRES. Clinical and radiographic data were collected. Descriptive statistics were used to determine the prevalence of corticosteroid therapy at the time of PRES onset and the latency from steroid initiation to PRES onset. The association between steroid therapy and extent of vasogenic edema was assessed in multiple regression models.

Results: We identified 99 cases of PRES in 96 patients. The median age was 55 years (IQR 30–65) and 74% were women. Steroid therapy at time of PRES onset was identified in 44 of 99 cases. Excluding patients on chronic therapy, the median duration of steroid exposure before PRES onset was 6 (IQR, 3–10) days. Steroid therapy was not associated with extent of vasogenic edema in unadjusted or linear and logistic regression models adjusted for age, sex, and maximum systolic blood pressure on day of onset.

Conclusion: Corticosteroid therapy, often of brief duration, frequently preceded the onset of PRES and was not associated with severity of vasogenic edema.

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a cerebrovascular syndrome characterized by acute neurological symptoms accompanied by typically reversible vasogenic edema [11,17]. Symptoms can include headache, confusion, vision changes, seizures, and focal neurological deficits [27]. At its core, PRES is thought to result from disordered or failed cerebrovascular autoregulation and is often preceded by hypertension [11,26,41]. An alternate model posits that PRES results from inflammation-mediated endothelial dysfunction [2].

PRES is associated with autoimmune disorders [10,21], bone marrow and solid organ transplantation [16,39,40], cancer [43], sepsis [3], and the peripartum state [4]. Corticosteroids are frequently used in many of these settings. Steroids are known to increase blood pressure [14,15] and therefore could precipitate PRES. However, steroids are also used in the treatment of vasogenic edema, such as in patients with intracranial mass lesions [9]. Case reports have implicated steroids as both the precipitant [5,8,12,19,20,23,24,30,31,34,38,47,48] and treatment [1,6,8,12,13,18,25,28,30,33,36,37] of PRES. Thus, the role of steroids in PRES remains unclear. We hypothesized that PRES is frequently preceded by initiation of corticosteroid therapy and aimed to assess the relationship between steroid therapy and the extent of vasogenic edema.

2. Methods

2.1. Study design

The overall design of our study has been previously described [42]. We conducted a retrospective cohort study of patients diagnosed with

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PRES at two tertiary-care academic medical centers in New York City: New York Presbyterian Hospital – Weill Cornell Medical Center (NYPH) and Memorial Sloan Kettering Cancer Center (MSK). NYPH is a certified comprehensive stroke center while MSK specializes in oncological care. Patients at MSK typically receive all of their care within the hospital system, and many NYPH patients similarly receive outpatient care in affiliated clinics. Both hospitals have inpatient and outpatient electronic medical records that facilitate detailed, longitudinal data review. Patients transferred to these institutions after presenting elsewhere were included if adequate clinical and radiographic data were available. Our study was approved by the institutional review boards of both institutions. All variables were defined in a data dictionary created by investigator consensus, and data were abstracted in standardized forms [46].

2.2. Study subjects

We performed a text search for "PRES" and "Posterior Reversible Encephalopathy Syndrome" of all brain magnetic resonance imaging (MRI) and computed tomography (CT) reports from 2008 to 2014. The entire reports, including the clinician-entered requisition, were searched. The study cohort was assembled from these screening results by identifying patients with brain parenchymal vasogenic edema on CT or MRI of the brain with associated neurological symptoms (headache, confusion, vision changes, seizures, and/or focal neurological deficits) that could not be attributed to other causes such as infection, malignancy, or stroke [11]. All available imaging studies, including subsequent studies, were available to the radiologist for review when assessing the index study. Patients were included in the cohort by consensus after review by both a neuroradiologist (ADS, RJY, AG) and neurologist (NSP, BBN). Patients under the age of 18 were included as there does not appear to be a distinct pediatric PRES phenotype; however, pediatric patients were excluded in sensitivity analyses [11].

2.3. Measurements

Patient demographics, comorbidities, and clinical and radiographic PRES characteristics were collected, including granular data regarding oncological history, vascular risk factors, and medication exposures. For incident cases of PRES, we abstracted PRES symptoms, vital signs, and laboratory values. The onset of PRES was defined as the day of symptom onset. The maximum systolic blood pressure on the day of onset was recorded. If symptoms began prior to admission, the maximum blood pressure on the day of admission was recorded. Detailed data regarding steroid therapy were collected including type, dose, duration, and indication for steroid therapy. Chronic steroid therapy was defined as steroid use for over 30 days. All steroid doses were adjusted by glucocorticoid potency relative to methylprednisolone [29].

2.4. Outcomes

The primary outcome was extent of vasogenic edema. A neuroradiologist (ADS) independently reviewed the initial imaging study to determine the number of areas with vasogenic edema as reflected either by CT hypoattenuation or MR T2 FLAIR hyperintensity. Diffusion-weighted imaging (DWI) was used to distinguish between vasogenic and cytotoxic edema. The presence or absence of mass effect, configuration (i.e. confluence), and reversibility on follow-up were used to distinguish between vasogenic edema and other causes of parenchymal T2 hyperintensity such as chronic ischemia, post-treatment change, and gliosis of other etiology. The extent of edema was defined as a continuous variable of 1 to 10 pre-defined regions: frontal, parietal, occipital, temporal, basal ganglia, thalamus, brainstem, cerebellum, deep white matter, and corpus callosum. This measure was developed in line with prior studies [22,35]. We also pre-specified a binary outcome in which edema in 1–4 regions constitutes moderate edema and edema in 5–10 regions constitutes extensive edema.

2.5. Statistical methods

Standard descriptive statistics were used to describe the patient population, PRES characteristics, and prevalence of steroid therapy at time of PRES. We compared patients receiving steroid therapy to patients with no steroid exposure using Chi-square or Fisher's exact test, as appropriate, for categorical variables and Student's *t*-test for numerical variables. Linear and logistic regression models, adjusted for age, sex, and maximum systolic blood pressure on day of onset, were used to assess the effect of steroid exposure on extent of vasogenic edema. Covariates were chosen a priori, and the number of covariates was limited to avoid over-fitting of models. We performed three sensitivity analyses. First, we limited the study cohort to patients 18 and older. Second, we excluded patients who had not undergone MRI. Third, we restricted analyses to patients with at least one repeat MRI available for comparison. Last, in an exploratory analysis, the Spearman correlation between steroid dose, relative to methylprednisolone, and number of areas of vasogenic edema was determined. All p-values were two-sided and evaluated at the 0.05 alpha level. All analyses were performed in SAS v9.3 (SAS Institute, Cary, NC).

3. Results

We identified 96 patients who met our final inclusion criteria after review of 179 records. Reasons for study exclusion were clinical histories inconsistent with PRES (48 patients), alternate radiological diagnoses (24 patients), and inadequate clinical information (11 patients). Two patients had more than one episode of PRES, such that our study cohort included 96 patients with 99 episodes of PRES; 94 of these 99 cases were diagnosed by MRI. In 64 (65%) cases, a repeat MRI was available for comparison.

Median patient age was 55 years (interquartile range [IQR], 30–65) with 10 patients being under the age of 18. Most patients (74%) were women. Of these 96 patients, 58% had active cancer, 28% had sepsis, 17% had a history of bone marrow transplantation, 1% had solid organ transplantation, 15% had an autoimmune disease, and 8% were peripartum. In 99 cases of PRES, the mean maximum systolic blood pressure on the day of onset was 180 (±32) millimeters mercury.

Corticosteroid therapy was noted at the time of PRES onset in 44 cases. In 10 cases, the patient was on chronic steroid therapy. In the remaining 34 cases, the median duration of steroid use before onset was 6 (IQR, 3–10) days, and 22 (50%) patients had started steroid therapy within 7 days. The most common indications were graft-versus-host disease, chemotherapy-associated indications, and stress-dose steroid dosing for shock. Patients on steroid therapy were more likely to have active cancer ($p = 0.02$) and to be receiving active chemotherapy ($p < 0.01$) or immunosuppressant medication ($p < 0.01$) than patients not receiving steroids (Table 1). However, as the short median duration of steroid therapy prior to PRES suggests, initiation of steroid therapy was a frequent proximate change in medical therapy. Treating clinicians explicitly attributed PRES to recent corticosteroid therapy in 5 of these 44 cases.

Patients with PRES had a mean of 4.4 (±2.2) brain areas of vasogenic edema with 39 cases (39%) having 5 or more areas with edema. In unadjusted analyses, there was no association between steroid therapy and extent of vasogenic edema when treated as a continuous or binary variable (4.5 [±2.0] areas in patients with steroid use versus 4.2 [±2.4] areas in patients without steroid use, $p = 0.50$) (Table 2). The results remained unchanged in multivariable linear and logistic models adjusting for age, sex, and blood pressure (data not shown). The results were also unchanged in sensitivity analyses limited to patients 18 years and older, cases diagnosed by MRI, and cases with at least one repeat MRI available for comparison (data not shown). Last, in an exploratory