

# Behavioral Effects of Corticosteroids in Steroid-sensitive Nephrotic Syndrome

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**ABSTRACT.** *Objectives.* The objective of this study was to define the frequency and severity of steroid-related behavioral side effects in children with steroid-sensitive idiopathic nephrotic syndrome (SSNS) during treatment for relapse.

*Study Design.* We conducted a prospective, repeated-measures study in which 10 children with SSNS underwent behavioral assessment using the Child Behavior Checklist at baseline and during high dose prednisone therapy for relapse.

*Results.* Of the 10 children, 8 had normal behavior at baseline. Of these 8 children, 5 had Child Behavior Checklist scores above the 95th percentile for anxious/depressive behavior and/or aggressive behavior during relapse. Such scores are in the range normally considered appropriate for referral to a mental health provider. The 2 children who had abnormal behavior at baseline also experienced a worsening of their behavior during relapse. The behavioral changes occurred almost exclusively at prednisone doses of 1 mg/kg every 48 hours or more. Regression analysis showed that prednisone dose was a strong predictor of abnormal behavior, especially increased aggression.

*Conclusion.* Children with SSNS often experience serious problems with anxiety, depression, and increased aggression during high-dose prednisone therapy for relapse. *Pediatrics* 1999;104(4). URL: <http://www.pediatrics.org/cgi/content/full/104/4/e51>; *nephrotic syndrome, prednisone, anxiety, depression, aggression, Child Behavior Checklist.*

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ABBREVIATIONS. SSNS, steroid-sensitive idiopathic nephrotic syndrome; CBCL, Child Behavior Checklist; PTSA, pooled time series analysis.

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The introduction of antibiotics and corticosteroids for the treatment of childhood nephrotic syndrome led to a dramatic decrease in both morbidity and mortality. It is now generally accepted that steroid-sensitive idiopathic nephrotic syndrome (SSNS) is a benign disease with a favorable prognosis overall.<sup>1</sup> However, 40% of children with SSNS will have a frequently relapsing course and many will be steroid-dependent.<sup>2</sup> Most attention to steroid toxicity

in childhood SSNS has focused on physical side effects, such as growth retardation, hypertension, obesity, and cataracts. Although the behavioral side effects of corticosteroid therapy in SSNS are acknowledged often, little is actually known about their clinical significance. In fact, the entire literature on steroid-related behavioral changes in children is sparse.<sup>3</sup> Case and group studies documenting effects of steroids on the mental status and behavior of children have reported dosage-related increased rates of depression and anxiety for children with asthma<sup>4,5</sup> and cancer.<sup>3,6</sup> However, studies vary widely in their use of assessment instruments, children in available studies often are taking multiple medications, and few studies use a prospective design, which would improve the reliability of results. The current study was undertaken to better define the frequency and severity of steroid-related behavioral changes in children with SSNS during relapse.

## METHODS

### Participants

Children with the diagnosis of SSNS were recruited from the Pediatric Nephrology Clinic at Doernbecher Children's Hospital at Oregon Health Sciences University. Fifteen English-speaking families with children ranging from 3 to 16 years of age agreed to participate. Five additional families declined participation. Reasons for not participating included lack of time and discomfort completing psychological surveys. There were no significant differences in demographic characteristics (ie, age and sex of child, duration of diagnosis, and parent marital status) between participants and nonparticipants. The majority of respondents were mothers (87%). A total of 10 participants completed the study. Of the 5 children who did not complete the study, 1 was rediagnosed as steroid resistant and 4 did not relapse during the 16-month course of the investigation. At entry, parental educational level, occupation, and marital status were determined. The Hollingshead Index of Social Class was used to calculate social status (A. B. Hollingshead, unpublished manuscript, 1975). The study protocol was approved by the institutional review boards at Oregon Health Sciences University and Washington State University. Informed consent was obtained from each child's parent or guardian.

### Design

A baseline measure of the child's behavior was completed by parents at a time when their child was in remission, off prednisone, or on low dose alternate day therapy (not >0.5 mg/kg every 48 hours). At the initiation of daily prednisone for relapse (2 mg/kg divided two times a day), the research staff conducted a series of telephone calls to assess the child's behavior. A round of five consecutive daily telephone calls was initiated 2 days after starting full dose prednisone and then repeated every 2 weeks for a total of four rounds of calls occurring during weeks 1, 3, 5, and 7 of therapy for relapse (20 calls total). The prednisone dose was decreased to 2 mg/kg every other day (single AM dose) at the time of urinary remission and then tapered ~0.5 mg/kg approximately every 2 weeks thereafter. Thus, the timing of behavioral assess-

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ments corresponded to the child's tapering medication schedule, depending on the timing of each patient's urinary remission. This prospective, repeated-measures study design allowed each child to act as his or her own control (baseline vs relapse behavior) and allowed assessment of dose-related changes in each child's behavior.

### Measures

At baseline, parents completed a full Child Behavior Checklist (CBCL).<sup>7,8</sup> The CBCL provides an age- and sex-standardized assessment of a child's behavior problems. It consists of 118 items assessing internalizing and externalizing behaviors. The CBCL is particularly useful because it allows for pooling and comparison of scores across the age range of our sample. To minimize parental fatigue, telephone assessments during relapse included only the anxiety/depression and aggression subscales of the CBCL. To test for defensive (socially desirable) responding, we examined the Defensive Responding (ie, socially desirable responding) subscale of the Parenting Stress Index,<sup>9</sup> which was also completed at baseline. Scores <10 are questionable. In our sample, the mean score was 15.4 ± 4.9, indicating valid responses.

### Statistical Analysis

Demographic data from participants and nonparticipants were compared by Fisher's exact tests and unpaired *t* test analyses. To test for the effect of individual variables on children's behavior during relapse, we conducted pooled time series analysis (PTSA). PTSA relies on a regression model in which serial observations (in this case, daily reports of child behavior) are combined (pooled) from the entire sample.<sup>10,11</sup> Thus, general time-related trends and individual differences can be tested in a small sample with multiple observations.<sup>12</sup> Patient age, baseline CBCL score, and prednisone dose were evaluated as predictors of abnormal behavior during relapse. The sample's overall heterogeneity in behavior was controlled by using between-subject difference codes in the regression analysis. Data were corrected for serial correlation and serial dependence.<sup>11,12</sup>

## RESULTS

### Baseline Demographics

Of the 10 participants, 8 (80%) were male. The mean age of the children was 8.2 years (range: 2.9–5 years). The average age at diagnosis was 4.3 years (range: 2–11 years), and the average duration of illness was 3.9 years (range: 6 months to 10.7 years). Of the 10 children, 9 were white, and 1 was black. Data on socioeconomic class were available for 9 of the 10 children who completed the study. There was 1 child in Hollingshead class I (highest), and 2 children each in classes II, III, IV, and V. All families completed telephone calls within 2 to 6 months of completing baseline measures.

### Steroid Dosing

Of the 10 children, 7 attained urinary remission by the second week of daily high dose prednisone and were on alternate day steroids by the second calling period (week 3). Two patients (patients 2 and 6; Table 1) did not attain urinary remission until the fourth week of daily high dose prednisone and were not on alternate day steroids until the third calling period (week 5). One patient (patient 1; Table 1) attained urinary remission by the second week of daily steroids but did not taper to alternate day therapy until the sixth week (parental error).

### Behavioral Assessments

At baseline, 80% (*n* = 8) of the children had CBCL scores in the average range, indicating that both their reported anxious/depressed behavior and their ag-

**TABLE 1.** Highest CBCL T Score and Prednisone Dose for Each Assessment Period for the Seven Children With Scores ≥95th Percentile During Relapse

| Patient Age and Gender  | Time Period of CBCL Assessment |        |        |        |        |
|-------------------------|--------------------------------|--------|--------|--------|--------|
|                         | Baseline                       | Week 1 | Week 3 | Week 5 | Week 7 |
| Patient 1: 2 y male     |                                |        |        |        |        |
| Anxiety/depression      | 68*                            | 88**   | 63*    | 61     | 52     |
| Aggression              | 68*                            | 100**  | 74**   | 58     | 68*    |
| Prednisone dose (mg/kg) | 0.5 AD                         | 2.0 D  | 2.0 D  | 2.0 D  | 1.5 AD |
| Patient 2: 3 y male     |                                |        |        |        |        |
| Anxiety/depression      | 40                             | 70**   | 50     | 50     | 50     |
| Aggression              | 50                             | 50     | 50     | 50     | 50     |
| Prednisone dose (mg/kg) | 0                              | 2.0 D  | 2.0 D  | 1.5 AD | 0      |
| Patient 3: 4 y male     |                                |        |        |        |        |
| Anxiety/depression      | 63                             | 66*    | 68*    | 50     | 50     |
| Aggression              | 65*                            | 75**   | 65*    | 50     | 58     |
| Prednisone dose (mg/kg) | 0.5 AD                         | 2.0 D  | 1.0 AD | 0.5 AD | 0      |
| Patient 4: 4 y male     |                                |        |        |        |        |
| Anxiety/depression      | 50                             | 57     | 61     | 61     | 63     |
| Aggression              | 50                             | 61     | 69*    | 64*    | 56     |
| Prednisone dose (mg/kg) | 0                              | 2.0 D  | 1.5 AD | 0.8 AD | 0.1 AD |
| Patient 5: 7 y female   |                                |        |        |        |        |
| Anxiety/depression      | 50                             | 62     | 52     | 50     | 50     |
| Aggression              | 50                             | 64*    | 63     | 50     | 50     |
| Prednisone dose (mg/kg) | 0                              | 2.0 D  | 2.0 AD | 1.4 AD | 1.0 AD |
| Patient 6: 7 y female   |                                |        |        |        |        |
| Anxiety/depression      | 50                             | 60     | 50     | 50     | 50     |
| Aggression              | 58                             | 73**   | 62     | 61     | 60     |
| Prednisone dose (mg/kg) | 0.3 AD                         | 2.0 D  | 2.0 D  | 2.0 AD | 2.0 AD |
| Patient 7: 9 y male     |                                |        |        |        |        |
| Anxiety/depression      | 50                             | 61     | 55     | 62     | 75**   |
| Aggression              | 50                             | 56     | 67*    | 65*    | 68*    |
| Prednisone dose (mg/kg) | 0                              | 2.0 D  | 2.0 AD | 1.6 AD | 1.2 AD |

\* >95th percentile, \*\* >98th percentile for age and gender.

D indicates daily; AD, alternate day.

gressive behavior were consistent with those of normal children. Of the children, 2 had baseline scores above the 95th percentile for both their anxious/depressed and aggressive behavior.

During relapse, 5 of the 8 children with normal baseline scores (62.5%) had CBCL scores above the 95th percentile for age and sex during at least one of the calling periods. In other words, the reported severity of abnormal behavior of these children was in the range normally considered appropriate for referral to a mental health provider. Of the children, 3 had elevated scores for both the anxiety/depression and aggression CBCL subscales, 3 children had elevated scores for only aggressive behavior, and 1 child had an elevated score for only the anxiety/depression subscale. The 2 children with abnormal behavior at baseline also exhibited a worsening of their behavior during relapse. Table 1 shows the highest CBCL score for each period during which behavior was assessed and the corresponding prednisone doses for each of the 7 patients who had CBCL scores above the 95th percentile during relapse (including the 2 children with abnormal baseline behavior). Tables 2 and 3 show the frequency with which each CBCL behavior item was reported.

PTSA indicated that behavioral symptoms increased across subjects, including those children whose behavior remained in the normal range during relapse ( $P < .0001$ ). PTSA showed that increased anxious/depressive symptoms during relapse were predicted by the baseline CBCL score ( $F = 16.69$ ;  $P < .005$ ), prednisone dose ( $F = 5.82$ ;  $P < .0001$ ), and between-subject effects ( $F = 8.09$ ;  $P < .0001$ ). The full set of predictors accounted for 44.5% of the variance with baseline scores, prednisone dose, and between-subject differences accounting for 7.8%, 14.5%, and 21.3% of the variance, respectively. Similarly, increased aggressive symptoms were predicted by the baseline CBCL score ( $F = 34.50$ ;  $P < .005$ ), the higher prednisone doses ( $F = 5.35$ ;  $P < .0001$ ), and between-subject effects ( $F = 3.24$ ;  $P < .01$ ). The full set of predictors for aggressive behavior accounted for 42.3% of the variance with baseline scores, prednisone dose, and between-subject differences accounting for 14.8%, 15.7%, and 9.0% of the variance,

**TABLE 2.** Frequency of Reported Anxious/Depressed Behaviors During Relapse

| CBCL Anxious/Depressed Behavior Item            | Occurs Sometimes or Frequently (%)* |
|---|-------------------------------------|
| Nervous, high strung, tense                     | 35                                  |
| Self-conscious, easily embarrassed              | 33                                  |
| Fearful or anxious                              | 27                                  |
| Unhappy, sad, depressed                         | 25                                  |
| Cries a lot                                     | 17                                  |
| Fears he or she might think or do something bad | 16                                  |
| Feels he or she has to be perfect               | 8                                   |
| Suspicious                                      | 8                                   |
| Feels others are out to get him or her          | 7                                   |
| Feels guilty                                    | 7                                   |
| Feels no one loves him or her                   | 5                                   |
| Feels worthless or inferior                     | 2                                   |
| Complains of loneliness                         | 1                                   |

\* Percentage of telephone calls in which the behavior was reported.

**TABLE 3.** Frequency of Specific Aggressive Behaviors Reported During Relapse

| CBCL Aggressive Behavior Item       | Occurs Sometimes or Frequently (%)* |
|-------------------------------------|-------------------------------------|
| Demands a lot of attention          | 52                                  |
| Sudden changes in mood              | 51                                  |
| Stubborn, sullen, irritable         | 46                                  |
| Argues a lot                        | 42                                  |
| Teases a lot                        | 39                                  |
| Temper tantrums or hot temper       | 39                                  |
| Disobedient at home                 | 39                                  |
| Gets in many fights                 | 35                                  |
| Cruelty, bullying, meanness         | 33                                  |
| Unusually loud                      | 33                                  |
| Talks too much                      | 29                                  |
| Screams a lot                       | 28                                  |
| Easily jealous                      | 18                                  |
| Physically attacks people           | 16                                  |
| Destroys things belonging to others | 15                                  |
| Threatens people                    | 10                                  |
| Disobedient at school               | 12                                  |
| Bragging, boasting                  | 8                                   |
| Destroys his or her own things      | 8                                   |

\* Percentage of telephone calls in which the behavior was reported.

respectively. Although young age was not a statistically significant predictor of abnormal behavior during relapse, it is notable that the 3 children whose behavior remained normal were  $\geq 10$  years of age.

## DISCUSSION

Our findings suggest that children with SSNS experience marked increases in behavior problems during relapse. On high dose prednisone, 7 of the 10 children studied had CBCL scores for anxiety, depression, and aggressive behavior above the 95th percentile for age. Such scores are in the same range as those of children who are referred to mental health services for disruptive behavior disorders and internalizing disorders such as depression and anxiety.<sup>7,8</sup> Of these 10 children, 2 had CBCL scores above the 95th percentile at baseline before any increase in prednisone dose. Both of these children experienced an intensification of their behavior problems on full dose prednisone. The observed behavioral changes occurred almost exclusively at the higher doses of prednisone (1 mg/kg every 48 hours or more). Regression analysis showed that prednisone dose was a strong predictor of abnormal behavior, especially increased aggressive behavior.

Previous pediatric studies on the mental status changes associated with corticosteroid therapy have been limited to children with asthma and hematologic malignancy.<sup>4-6,13,14</sup> These studies found disturbances in affect, behavior, and intellect. Specifically, depression, anxiety, euphoria, irritability, restlessness, withdrawal, sleep difficulties, and disturbances in memory have been described. However, the co-administration of medications with behavioral side effects (such as theophylline and chemotherapy) complicates the interpretation of previous results.

The magnitude of the behavioral disturbances found in our patients necessitates parental preparation for significant difficulties in caring for children with SSNS during high dose steroid therapy. Chil-

dren <10 years of age may be particularly challenging, especially those children with baseline abnormalities in their behavior. Furthermore, other factors during relapse, such as discomfort from anasarca, may contribute to behavioral problems during relapse, leading to even greater difficulty in caring for these children. It is possible that the parents whose children experience serious steroid-induced behavioral side effects may have been more likely to consent to this study, thereby increasing the magnitude of behavioral problems that were found. However, the effect of this potential bias is likely to be minimal, because 75% of eligible subjects participated.

The mechanism by which corticosteroids affect behavior is likely multifactorial. Corticosteroid receptors, located densely throughout the hippocampus, septum, and amygdala areas of the brain, are believed to be intimately involved in behavior, mood, and memory. In addition, corticosteroids have been shown to alter brain excitability and to affect central nervous system levels of certain neuropeptides and neurotransmitters.<sup>16</sup> Pharmacokinetic studies of children with nephrotic syndrome demonstrate increased serum levels of unbound (free) serum prednisolone during periods of hypoalbuminemia.<sup>17,18</sup> In a previous report, major steroid side effects were found to be more likely in adult patients with chronic active hepatitis and hypoalbuminemia compared with similar patients with normal serum albumin. The increased side effects in the hypoalbuminemic patients were attributed to higher levels of unbound serum prednisolone.<sup>19</sup> We speculate that children with nephrotic syndrome in relapse are especially vulnerable to serious steroid-induced behavior disturbances during periods of hypoalbuminemia attributable to increased levels of prednisolone in the central nervous system. Serum albumin levels and degree of edema were not recorded in our patients.

The best treatment for steroid-induced behavior disturbance is to taper the steroids to the lowest dose possible or to discontinue the use of steroids altogether. Although it is common practice during relapse to begin tapering prednisone on urinary remission, the dosing of prednisone during the initial presentation of SSNS is quite different. Many practitioners prescribe an 8-week steroid regimen (60 mg/M<sup>2</sup> per day for 4 weeks followed by 40 mg/M<sup>2</sup> each alternate day for 4 weeks) based on the International Study of Kidney Diseases in Children.<sup>20</sup> More recently, some investigators have advocated lengthening this regimen to 12 weeks (60 mg/M<sup>2</sup> per day for 6 weeks followed by 40 mg/M<sup>2</sup> each alternate day for 6 weeks) to promote a higher proportion of sustained remissions.<sup>21</sup> Thus, the steroid regimen for children with SSNS at presentation often consists of high dose prednisone for a longer period, compared with the steroid regimen during a subsequent relapse. Therefore, parents need to be warned of the potential for an extended period of difficult behavior during treatment for the initial episode.

### CONCLUSION

In summary, children with SSNS often experience significant problems with anxiety, depression, and

increased aggression during high dose steroid therapy. Children with frequent relapses are at risk for repeated episodes of difficult behavior. Parents should be advised in advance about the potential magnitude of these side effects. Appropriate warning hopefully will allow families to be better prepared for behavior problems both at home and at school while their child is on high dose prednisone. Additional research on interventions to diminish steroid-associated behavioral changes is needed.

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