Glucocorticoids in the Treatment of Children with Acute Lymphoblastic Leukemia and Hodgkin’s Disease: A Pilot Study on the Adverse Psychological Reactions and Possible Associations with Neurobiological, Endocrine, and Genetic Markers

Rosemarie Felder-Puig,1 Christiane Scherzer,1 Michaela Baumgartner,1 Magdalena Ortner,1 Claudia Aschenbrenner,1 Christian Biegelmayer,2 Till Voigtlander,3 E. Renate Panzer-Grunmayer,5 Wim J.E. Tissing,6,8 Jan W. Koper,7 Karl Steinberger,1 Christian Nasel,4 Helmut Gadner,1 Reinhard Topf,1 and Michael Dworzak1

Abstract

Purpose: We did a controlled study to assess adverse psychological reactions (APR) associated with high-dose glucocorticoid therapy and tried to detect somatic correlates for the observed reactions.

Patients and Methods: Our study included 37 patients with acute lymphoblastic leukemia (ALL) and 11 patients with Morbus Hodgkin (MH) disease, who were treated with high-dose glucocorticoid therapy, and 26 control patients with other types of malignancies. APRs were assessed with a standardized measure via parent-report. Patients with ALL and MH were further analyzed for signs of neuronal cell death in the cerebrospinal fluid, polymorphisms of the glucocorticoid receptor gene, as well as cortisol, adrenocorticocorticotropic hormone, and dehydroepiandrosterone sulfate blood levels.

Results: Fifty-four percent of ALL, 36% of MH, and 23% of control patients developed APR in the first few weeks of therapy. Approximately 3.5 months later, the majority of patients with ALL showed no APR, similar to control patients. Patients demonstrating a higher, nonsuppressible secretion of cortisol and/or adrenocorticocorticotropic hormone during glucocorticoid therapy were found to be more likely to develop APR. No sign of neuronal cell destruction and no correlation of APR with specific glucocorticoid receptor polymorphisms were found.

Conclusion: Our results suggest that the development of APR due to glucocorticoid therapy is measurable and correlates with hormonal reaction patterns.

Glucocorticoids play an important role in the treatment regimens of pediatric patients with acute lymphoblastic leukemia (ALL) and Morbus Hodgkin (MH) disease. Their therapeutic efficacy is well established, but their use is associated with various side effects and psychodynamic changes. Potential adverse effects include altered fat distribution (Cushing-like), obesity, hypertension, gastritis, diabetes mellitus, myopathy, avascular necrosis of joints, osteopenia, hepatomegaly, immune suppression with a resultant increase in infections, and others (1–4). High-dose glucocorticoid therapy also renders patients emotionally unstable resulting in presentations of extreme mood changes, states of anxiety, depressive mood, psychoses, as well as disturbed eating habits with uncontrollable eating episodes. Although these adverse psychological reactions (APR) might be present during all stages of cancer treatment, they seem to occur most frequently and intensively during high-dose glucocorticoid therapy.

A recently published review could not provide any reliable estimates for incidence or prevalence of these effects nor clear risk factors (5). Stuart and colleagues identified 16 case reports of severe APR due to glucocorticoid therapy, over half of which included psychotic symptoms. From the described cases, they concluded that most severe APR appeared shortly after the commencement of glucocorticoid therapy, resolved swiftly on dose reduction or cessation of glucocorticoid treatment, and reappeared on dose increase.

It is still unclear whether the degree of APR occurs as an effect of individual predisposing factors, environmental stresses, or the pharmacokinetic properties of the exogenous glucocorticoids, nor if these disturbances have measurable physiologic...
correlates. There has been a long-recognized association between excessive endogenous corticosteroid levels caused by severe stress and altered mood and behavior (6–11). Continuous hypersecretion may induce degeneration and depletion of neurons in the hippocampus, which, as part of the limbic system, is involved in the regulation of emotions. Sustained exposure to exogenous glucocorticoids may also cause hippocampal damage, although it is unclear whether exogenous glucocorticoids gain access to the same cellular sites as those occupied by endogenous glucocorticoids (12–14).

High-dose glucocorticoid therapy results in the suppression of the hypothalamic-pituitary-adrenal (HPA) axis (15, 16). Adrenal suppression may be related to the duration of therapy, type of steroid used and dosage, and schedule of glucocorticoid administration, but empirical data are controversial. It is also possible that there are individual differences in the extent of adrenal suppression that are associated with different degrees of severity of APR.

The degree of APR may be also caused by genetic predisposition. Altered responsiveness of glucocorticoids has been described due to polymorphisms of the glucocorticoid receptor gene. The ER22/23EK polymorphism results in decreased sensitivity for glucocorticoid (17), whereas two other polymorphisms (N363S and Bcl1) have been associated with an increased glucocorticoid sensitivity as measured with a dexamethasone suppression test in asymptomatic healthy adults (18–20). The clinical relevance of the increased sensitivity for glucocorticoid in relation to the N363S polymorphism remains controversial (21–25), but the Bcl1 polymorphism has been related to a higher body mass index, abdominal obesity, and higher systolic blood pressure (18, 26, 27). However, in a recent study, these polymorphisms were not related to glucocorticoid sensitivity in childhood ALL cells (28).

It would be desirable to get more insight into the nature of APR during glucocorticoid therapy and their underlying mechanisms, to detect somatic correlates for the observed reactions, and to find out if the possible damage is reversible. Therefore, we conducted a pilot study addressing the following questions:

What is the prevalence of APR in pediatric cancer patients treated with high-dose glucocorticoid therapy as compared with those receiving no glucocorticoid therapy?
Do specific patterns of endocrine hormone levels [cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S)] during glucocorticoid therapy increase the liability for APR?
Are there any associations between APR and neuronal cell death, if detectable?

Are there any associations between APR and specific polymorphisms?
Are APR and abnormal eating behavior completely reversible after discontinuation of glucocorticoid therapy or do they persist to some degree?

## Patients and Methods

The study was conducted in Austria’s largest center for the treatment of childhood cancer. It opened in 2003 for the recruitment of consecutive patients who were referred for cancer treatment to our hospital and who met the following criteria: patients ages 4 to 18 years, parents fluent in the German language, and informed consent provided by parents and older children and adolescents. The study protocol received approval from our Institutional Ethics Committee.

For analysis, the patients were divided into three groups: the ALL group (37 patients), the MH group (11 patients), and the control group (26 patients with other types of malignant disease). Patients’ characteristics are detailed in Table 1. Although the ALL and control group were not significantly different in terms of age and gender, there were more female and older patients in the MH group. Because the MH sample was small, results in this group have to be interpreted with caution.

Patients with ALL received treatment according to the Associazione Italiana Ematologia Oncologia Pediatrica-BFM ALL 2000 trial, which is a modification of former Berlin-Frankfurt-Münster type protocols (29–31). It includes continuous high-dose oral glucocorticoid therapy for 4 weeks: after a 7-day prephase with daily oral prednisolone, patients <10 years of age were randomized to receive either 60 mg/m² of prednisolone or 10 mg/m²/day of dexamethasone body surface area/d until day 28. Patients ≥10 years received prednisolone only. In total, 25 patients received prednisolone and 12 received dexamethasone. Additional polychemotherapy during the glucocorticoid period consisted of L-asparaginase, daunorubicin, and vincristine. After day 28, steroid medication tapered over 9 days, but chemotherapy was continued for an additional 4 weeks with 6-mercaptopurine, cyclophosphamide, and low-dose cytarabine. Day 78 onwards, patients received interval treatment with 6-mercaptopurine and high-dose methotrexate with folate rescue. All patients also received intrathecal therapy with methotrexate (age-adjusted) on days 1, 12, 33, 45, 59, and along with each high-dose methotrexate.

The MH group received a pulsed high-dose glucocorticoid therapy (2 weeks each on/off of 60 mg/m²/day of oral prednisolone for two cycles and 40 mg/m²/day thereafter for two additional cycles—in total, 8 weeks of glucocorticoid therapy). Glucocorticoid therapy was given as part of the chemotherapy regimen according to current protocols GPOH-HD 95+03 (32, 33), prescribing two to six blocks of stage-adjusted polychemotherapy. Briefly, two 15-day OPPA/OEPA blocks (containing vincristine and procarbazine for girls only, and etoposide for boys only, prednisolone, and Adriamycin) were followed by two to four COPP cycles (cyclophosphamide, vincristine, procarbazine, and prednisolone).

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALL group</th>
<th>MH group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>37</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Male, 59.5; female, 40.5</td>
<td>Male, 36.4; female, 63.6</td>
<td>Male, 69.2; female, 30.8</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>9.27 (3.96)</td>
<td>14.27 (2.45)</td>
<td>10.73 (4.90)</td>
</tr>
<tr>
<td></td>
<td>Range, 4-18</td>
<td>Range, 10-18</td>
<td>Range, 4-18</td>
</tr>
<tr>
<td>Diagnoses in control group</td>
<td>6 rhabdomyosarcoma, 5 Wilm’s tumor, 4 Ewing’s sarcoma, 4 osteosarcoma, 3 AML, 2 CML, 1 epithelioid tumor, 1 hepatoblastoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Control patients had chemotherapy for various types of malignancies, but without any glucocorticoid treatment. Based on the regimens, psychological assessment took place at the following time points:

- at baseline (week 1) in all three groups
- at week 5 in ALL group (after 4 weeks of continuous glucocorticoids)
- at week 5 in the control group
- at week 7 in the MH group (after two 2-week cycles of glucocorticoids disected by 2 weeks of stopp)
- at weeks 17 to 19 in all three groups (ALL, at the end of interval treatment; MH, before the third COPP cycle).

### Psychological assessment.

For the assessment of APR, we chose the “Child Behavior Checklist” (CBCL), which is one of the most widely used measures in child psychology (34). It assesses the child’s behavior via parent-report. The scores are normed separately for boys and girls and for younger and older children, based on a nationally representative sample. A large number of studies support the reliability and the construct- and criterion-related validity of the instrument. Recently, a meta-analysis confirmed that the CBCL is useful for diagnosis in child psychiatry, for example, in distinguishing bipolar from attention deficit/hyperactivity disorder subjects (35). From the eight available CBCL scales, we selected the following five scales which seemed appropriate for our purposes and our setting: withdrawn, anxious/depressed, thought problems, attention problems, and aggressive. For every scale, the cutoff scores between normal, borderline, and clinical range were based on the study of large normative samples and can be found in the test manual. We determined APR in patients if they had a CBCL score in the clinical range in at least one of the five scales.

To minimize possible sources of bias when using parent-reports, which may be caused by the shock of diagnosis, the need for hospitalization, chemotherapy, or parents’ anxiety and distress, we compared classifications based on CBCL scores (APR versus no APR) measured at two consecutive time points, for example, at baseline and at week 5, and elaborated a categorization of APR, which is displayed in Table 2. To give an example, the category of “type 1” means that all CBCL scale scores of the individual patient were in the normal or borderline range at time point 1, while they were in the clinical range in at least one of the CBCL scales at time point 2.

Abnormal eating behavior and particular family distress are two other phenomena that are clinically observed in patients receiving glucocorticoid therapy. Because we could not find any standardized German-language measures to assess those variables, we designed a questionnaire containing 11 items addressing a specific eating pattern, and 17 items covering problems that primary caregivers and families of patients may face during therapy. The items of this self-designed questionnaire are shown in the Results (Table 4). The CBCL scales and the self-designed questionnaires had to be completed by the accompanying parents of all included patients at the previously defined measurement time points.

### Assessment of hormone levels.

Adrenal and pituitary hormone levels in patients with ALL and MH were measured using the venous blood samples collected from patients in the early morning. Samples were kept at 4°C immediately after collection until analysis. Serum cortisol concentrations (µg/dL) were measured by dissociation-enhanced lanthanide fluoroimmunoassay with an Auto-DELFIA analyzer using kits from Wallac Oy. Concentrations of ACTH (pg/mL) in EDTA plasma were analyzed by chemiluminescent immunoassays on an Advantage system from Nichols Institute Diagnostics. An electrochemiluminescent immunoassay method running fully automated on a Modular Analytics system from Roche, served for the determination of DHEA-S levels (µg/mL).

We derived the upper quartile, the upper tertile, and the median values as cutoff points to determine high versus lower endogenous steroid activity at week 5 for the ALL group and at week 7 for the MH group. We hypothesized that elevated cortisol and/or ACTH levels during glucocorticoid therapy are associated with a higher degree of APR in patients. The secretion of the adrenal hormone DHEA-S might possibly have a moderating effect on the patients’ status. A major limitation in testing this assumption in our sample was that concentrations of DHEA-S vary with age and hardly manifest in children below the age of 10.

### Assessment of neuronal cell destruction.

14-3-3 proteins are major evolutionarily conserved cystosolic proteins that regulate signal transduction, apoptosis, and neurotransmitter synthesis. Cerebrospinal Fluid (CSF) levels of 14-3-3 protein may be valuable markers of early neuronal cell destruction. For example, detectable levels of 14-3-3 in the CSF have been shown in patients with recent ischemic stroke, transverse myelitis, herpes simplex encephalitis, and Creutzfeld-Jakob disease (36–39). To test for the relationship between neuronal cell destruction and psychopathology, the CBSP of patients with ALL, which was routinely collected by lumbar puncture at diagnosis as well as on days 12 and 33 of glucocorticoid-containing induction therapy was assessed for elevated levels of 14-3-3. Briefly, an equivalent of 20 µL of CSF per sample was separated by denaturing SDS-PAGE at 30 V for the first hour and at 70 V for the subsequent 3 h using a premanufactured 16% resolving gel (Novex; Invitrogen). After transferring to a polyvinylidene difluoride membrane (Immobilon; Millipore Corporation), the membrane was blocked in 5% fat-free milk solution overnight to prevent any nonspecific binding. Subsequently, immunostaining was done by the sequential incubation of the membrane with a rabbit polyclonal anti-human 14-3-3σ antibody (1:500 dilution; Santa Cruz Biotechnology) and a peroxidase-conjugated polyclonal swine anti-rabbit antibody (1:500 dilution; DAKO). Specific antigen binding was detected using a chemoluminescence kit (Super Signal; Pierce Biotechnology) and ECL Hyperfilm (Amersham Biosciences) according to the manufacturer’s protocols. In case of positive results, further analyses should evaluate their association with APR.

### Genotyping.

To genotype the different patient samples, allelic discrimination was done with TaqMan Universal PCR master mix, primers, and probes (Applied Biosystems) and a TaqMan ABI Prism 7700 Sequence Detection System as previously described (18). The reaction components and amplification variables were based on the instructions of the manufacturer with an annealing temperature of 60°C and optimized concentrations for primers of 400 nmol/L for each polymorphism. The primers and probes used for the analysis are listed in Table 3. We reanalyzed the genotypes of all heterozygous and homozygous carriers of the polymorphisms and found identical genotypes.

### Statistical analyses.

Due to the small sample sizes, we primarily analyzed our data for descriptive characteristics. To test for group differences, odds ratios and 95% confidence intervals (95% CI) were calculated from crosstabs, or unpaired, two-tailed Student’s t tests were
done. All computations were done using the SPSS 11.0 statistical package for Apple Macintosh.

Results

**Short-term psychological effects of glucocorticoid therapy.** Analyzing the assessments of the first two time points (week 1 and weeks 5–7), patients with a type 1 profile (explained in Table 2) were significantly more prevalent in the ALL group than in the control group (54% versus 23%; odds ratio, 3.9; 95% CI, 1.3–12.0)—see Fig. 1. In the MH group, 36% of patients were identified as type 1. Combining type 1 and type 3 profiles, ~70% of ALL, 45% of MH, and 42% of control patients showed some kind of APR at weeks 5 to 7. Most type 1 patients in the ALL group showed thought problems and/or social withdrawal symptomatology, whereas thought problems and/or anxiety/depression were more prevalent in the MH group. In the control group, patients most frequently exhibited anxious/depressive symptoms.

Table 4 displays the items of the self-designed questionnaire completed by parents. In a substantial number of items, patients with ALL showed significantly higher scores than patients with ALL and were almost similar to control patients in terms of excessive eating behavior at week 5. Patients with MH seemed to exhibit fewer abnormal eating behaviors than patients with ALL and were also similar to controls. Regarding caregiver/family distress, our hypothesis that the families of children who receive glucocorticoid therapy could be more prevalent among the three groups at week 19 (see Table 4).

**Long-term psychological effects of glucocorticoid therapy.** At week 5, APR had been shown in 70% of patients with ALL, and by week 19, it resolved in 54% whereas it persisted in 16%. Approximately 45% of patients with MH showed APR at week 19, about half of which was already prevalent in week 7, whereas the other half developed after week 7. Another 36% of the MH group had no problems at either week 7 or at week 19. More than half of the control patients showed no APR at week 5 or 19. Of the 42% of control patients who had shown some kind of APR at week 5, it resolved in about half of which it persisted in the other half. The distribution of patients showing no signs of APR at week 19 was almost equal in all the ALL and control group (76% versus 69%; odds ratio, 1.38; 95% CI, 0.5–4.2). Almost no differences in eating patterns could be observed among the three groups at week 19 (see Table 4).

**Association between APRs and hormone levels.** The interindividual variations in endocrine hormone levels in patients with ALL at week 5 (before the end of glucocorticoid therapy) were large: the values for cortisol were 0.4 to 29.9 μg/dL; median, 1.6; and for ACTH, 3.0 to 56.0 pg/mL; median, 7.0. The results of cortisol and ACTH analyses in comparison with APR profiles for the ALL group at week 5 are displayed in Tables 5 and 6. Spearman’s rank correlation between cortisol and ACTH values was 0.50, representing a moderate association between cortisol and ACTH levels. The distribution of patients that scored above the group median for both cortisol and ACTH was 9 of 20 (45%) type 1 patients, 2 of 8 (25%) type 2 patients, and 1 of 6 (17%) type 3 patients. An additional seven type 1 patients scored above the group median of either cortisol or ACTH. The odds for type 1 patients to show a cortisol and/or ACTH level above the upper tertile (cortisol, 4.1 μg/dL; ACTH, 9.0 pg/mL) was 67%, whereas it was 14% to 22% for patients of types 2, 3, or 4 (odds ratio, 5.0; 95% CI, 0.9–28.1). Levels of cortisol and/or ACTH were not associated with the type of glucocorticoid (dexamethasone or prednisolone). No specific pattern could be identified for the role of the hormone DHEA-S in patients aged ≥10 years. Descriptive statistics for DHEA-S in the ALL group were 0.15 to 2.12 μg/mL; median, 0.31.

In the MH group, the large interindividual variation of adrenal suppression was more evident for ACTH than for cortisol. Due to the small sample size, no analyses comparing elevated hormone levels and APR profiles could be made. Descriptive statistics were: cortisol—range, 4.8 to 27.8 μg/dL; median, 13.0; ACTH—range, 2.3 to 74.0 pg/mL; median, 6.0; DHEA-S—range, 0.27 to 1.62 μg/mL; median, 0.49.

**Association between APRs, neuronal cell destruction, and specific polymorphisms.** To start with, 72 CSF samples of

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Primers</th>
<th>Probes</th>
<th>Concentration (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N363S</td>
<td>Fw 5'-CAACAGCGAGATCAAGAAGCGTAT-3'</td>
<td>Wt 5'-FAM-CCTATTCCAAATTTTCGGAAACCAACGG-3'</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Rev 5’-GCCGAGCAATTCGCTTACG-3'</td>
<td>Mu 5’-VIC-CCTACATCCAACTTCGGAACCAACGG-3'</td>
<td>100</td>
</tr>
<tr>
<td>ER22/23EK</td>
<td>Fw 5’-TCCAAAGAAAATCCTAGTGA-3’</td>
<td>Wt 5’-FAM-ACATCTCCCTCTTCTGAGCAAGC-3’</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Rev 5’-GCCCTCTCCTCCTGAGTTTATAGAAG-3’</td>
<td>Mu 5’-VIC-ACATCTCCCTCTTCTGAGCAAGC-3’</td>
<td>100</td>
</tr>
<tr>
<td>BclI</td>
<td>Fw 5’-GGTCAACAGGGTTTCTGTTATA-3’</td>
<td>Wt 5’-FAM-TCTGCTGTAATCT-3*</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Rev 5’-TTGCACCCATGGTGACACCAAT-3’</td>
<td>Mu 5’-VIC-TCTGCTGTAATCT-3*</td>
<td>50</td>
</tr>
</tbody>
</table>

*Minor groove-binding probes.

NOTE: Concentrations are indicated for the probes. Fw, forward; Wt, wild-type; Rev, reverse; Mu, mutant.

Fig. 1. Psychological categorization according to CBCL results at week 1 and weeks 5 to 7. Prevalence of the four APR profiles in ALL, MH, and control (CG) groups. For explanation of the four types, see Table 2.
18 patients of the ALL group were assessed for the presence of the 14-3-3 protein. Only one sample, taken directly after diagnosis, was positive for 14-3-3 (almost at the detection limit of our assay system). Thus, no evidence of an association between APR due to glucocorticoid therapy and neuronal cell death could be found, and we closed the study at this point for the assessment of neuronal cell destruction. Likewise, no correlation between the polymorphisms ER22/23EK, N363S, and Bcl1 and an increased risk for APR could be found in the 37 ALL patient samples.

**Dexamethasone versus prednisolone and APRs.** Of the 12 patients receiving dexamethasone and the 25 patients receiving prednisolone in the ALL group, there were 8 patients (67%) with type 1 profiles in the dexamethasone group and 12 patients (48%) with type 1 profiles in the prednisolone group. Odds ratio for the development of APR when treated with dexamethasone was therefore 2.2. With a 95% CI of 0.5 to 9.1, this risk is, however, not significant.

Analyzing item scores of abnormal eating behavior in patients with ALL, patients receiving dexamethasone scored significantly higher (in terms of more problems) for “Seems to be hungry all the time” and “Angry when not getting desired food” as compared with patients receiving prednisolone. Mean differences in another five items of this questionnaire failed to reach statistical significance but seemed to be in the same direction.

### Discussion

In this study, we attempted to examine the incidence of APR resulting from glucocorticoid therapy in pediatric patients with ALL or MH. Psychological assessment of patients during intensive therapy is difficult. The overlap of symptomatology, the fact that sadness and psychological distress are to some extent normal and expected reactions to a diagnosis of cancer, the patients’ unwillingness or inability to disclose emotional problems, and parent-reports biased by fears and uncertainty complicate the collection of valid data. To rule out some possible sources of bias, we chose a standardized and validated measure for the assessment of APR, used a control group receiving no glucocorticoid therapy, and elaborated a categorization system based on psychological scores collected at two consecutive measurement time points. In our cohort of patients with ALL, significantly more patients showed APR at week 5 of therapy as compared with control patients (54% versus 23%). Of the patients with MH, who were treated with another glucocorticoid treatment regimen than patients with ALL, 36% were identified as having developed APR in the course of glucocorticoid treatment. The most commonly occurring syndromes in the ALL sample were thought problems and withdrawal; in patients with MH, thought problems and anxiety/depression; and in the control group, anxiety/depression. We found the CBCL well suitable for our purposes, but we cannot rule out that there are better measures to be applied for the assessment of APR in this setting.

Most previous research on APR focused on descriptions of dramatic behavioral reactions reported in case series and case reports (5). There are also some controlled prospective trials providing information on less severe glucocorticoid-induced APR, but most of them focused on nonneoplastic conditions (5, 40). In the U.K. Medical Research Council ALL97 randomized trial comparing treatment with dexamethasone versus prednisolone, of all adverse side effects of glucocorticoid therapy, acute behavioral disturbance had the highest incidence (4). Still, only 58 of 1,603 (3.6%) patients were affected, which is a much lower incidence than reported in our study. The difference may be explained by the different assessment tools used. In the ALL97 randomized clinical trials, clinicians were probably asked to report only problems of a degree of severity that led to a cessation of glucocorticoid therapy or to an alteration of the glucocorticoid regimen, whereas in our study, professionals had to answer to which extent each of the 230 symptoms was present.

### Table 4. Individual items of questionnaire and significant differences (P ≤ 0.05) between group responses at weeks 5 to 7

<table>
<thead>
<tr>
<th>Abnormal eating behavior of patient</th>
<th>ALL &gt; CG, ALL &gt; MH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takes mainly liquids (tea, soup, etc.)</td>
<td>ALL &gt; CG, ALL &gt; MH</td>
</tr>
<tr>
<td>Gets up at night to drink</td>
<td>ALL &gt; CG, MH &gt; CG</td>
</tr>
<tr>
<td>Seems to be hungry all the time</td>
<td>ALL &gt; CG, MH &gt; CG</td>
</tr>
<tr>
<td>Eats more than usually</td>
<td>ALL &gt; CG, MH &gt; CG</td>
</tr>
<tr>
<td>Wants to eat when seeing others eat</td>
<td>ALL &gt; CG</td>
</tr>
<tr>
<td>Hard to stop eating</td>
<td>ALL &gt; MH</td>
</tr>
<tr>
<td>Fastidious, eating only selected food</td>
<td>ALL &gt; CG</td>
</tr>
<tr>
<td>Eating with passion</td>
<td>ALL &gt; MH</td>
</tr>
<tr>
<td>Angry when not getting desired food</td>
<td>ALL &gt; MH, CG &gt; MH</td>
</tr>
<tr>
<td>Always eating up</td>
<td>ALL &gt; CG</td>
</tr>
<tr>
<td>Family spends more money for child’s food</td>
<td>ALL &gt; CG</td>
</tr>
</tbody>
</table>

### Caregiver/family distress

| NOTE: Caregivers had to answer to which extent statement was | ALL > MH, CG > MH |
| Caregiver feels tense | ALL > MH, CG > MH |
| Caregiver feels tired | ALL > MH, CG > MH |
| Caregiver feels irritable | ALL > MH, CG > MH |
| Caregiver feels good | ALL > MH, CG > MH |
| Caregiver suffers from family disputes | ALL > MH, CG > MH |
| Caregiver feels helpless because of child’s behavior | ALL > MH, CG > MH |
| Caregiver feels challenged by child’s behavior | ALL > MH, CG > MH |
| Caregiver is worried about child’s behavior | ALL > MH, CG > MH |
| Hard for caregiver to get along with child | ALL > MH, CG > MH |
| Caregiver suffers from child’s aggressive behavior | ALL > MH, CG > MH |
| Child tries to derive an advantage from situation | ALL > MH, CG > MH |
| Caregiver and her/his partner argue about the child more often than usually | ALL > MH, CG > MH |
| Child is aggressive only towards caregiver | ALL > MH, CG > MH |
| Family suffers from child’s aggressive behavior | ALL > MH, CG > MH |
| Caregiver gets support from her/his partner all the time | ALL > MH, CG > MH |
| Child has disputes with siblings | ALL > MH, CG > MH |
| Caregiver is worried about child’s changed character | ALL > MH, CG > MH |
|

randomized trial comparing treatment with dexamethasone versus prednisolone, of all adverse side effects of glucocorticoid therapy, acute behavioral disturbance had the highest incidence (4). Still, only 58 of 1,603 (3.6%) patients were affected, which is a much lower incidence than reported in our study. The difference may be explained by the different assessment tools used. In the ALL97 randomized clinical trials, clinicians were probably asked to report only problems of a degree of severity that led to a cessation of glucocorticoid therapy or to an alteration of the glucocorticoid regimen, whereas in our study,
all APRs, including those that could be well handled by parents and/or the health care team, were registered. According to our experience, one-to-one nursing with mental health–trained staff, limiting stimuli and special support of the patient’s family is the strategy that has proven to be most valuable for getting through this treatment period. In difficult cases, we consult a child and adolescent psychiatrist for the prescription of psychoactive medication. There is no evidence yet in the literature that would suggest which strategies might work best in the pediatric population (5, 40).

The patients with ALL showed significantly more excessive eating behavior than the control group at week 5. This difference could not be found for the patients with MH. Caregiver/family distress was similar in all three groups, which is probably an effect of the individualized and extensive information about oncoming challenges all parents receive when the therapy begins.

At week 19, ~3 to 4 months after the termination of high-dose glucocorticoid therapy, the majority of patients with ALL who had exhibited APR at week 5 seemed to be back "normal". Only ~16% of patients with ALL still showed psychological disturbance, which was a similar rate to that seen in the control group (~23%). In the MH group, ~45% showed APR in week 19, half of which was already prevalent in week 7, whereas the other half only developed since week 7. It seems that the risk for APR in patients with MH gradually develops due to the continued pulsed glucocorticoid therapy in MH.

Two large randomized clinical trials recently compared the outcome variables of treatment with dexamethasone versus prednisolone and found that dexamethasone was more favorable in terms of event-free survival, but had higher toxicity including a higher risk for acute psychopathologic reactions (3, 4). In our small sample of patients with ALL, a trend towards more APRs following treatment with dexamethasone could be observed as well. Treatment with dexamethasone seemed to induce abnormal eating behaviors to a higher extent than treatment with prednisolone. In a study done in a Saudi Arabian center, the 4-week dexamethasone treatment led to a significant increase in weight compared with what was observed in patients receiving prednisolone (2). These results can be useful for the discussion of whether prednisolone should be substituted with dexamethasone in future protocols.

There has been considerable focus on hippocampal damage as a potential mechanism underlying the adverse psychological effects of glucocorticoid therapy (5). In an attempt to find somatic correlates that may have the power to confirm or even predict the psychological effects, we analyzed the CSF of patients with ALL to detect signs of neuronal cell death. In this respect, the 14-3-3 protein immunoassay on CSF is routinely used as a diagnostic tool in several diseases of the central nervous system (36–39, 41). The 14-3-3 protein isofoms are physiologically expressed in various tissues, and their presence in the CSF reflects extensive destruction of brain tissue, particularly in superficial brain structures such as the cortical gray matter. In our study, the 14-3-3 protein was found in only 1 of 72 CSF samples at an unexpected time point, right after diagnosis of the disease. Thus, we may conclude that glucocorticoid therapy does not induce neuronal cell destruction to an extent that it can be detected with the 14-3-3 protein assay.

Steroid hormones contribute to shaping behavioral function during early development and act as risk factors for psychopathology. An altered negative feedback control of the HPA system and cortisol hypersecretion have consistently been detected in patients with major depressive disorders (5, 42, 43). High-dose glucocorticoid therapy usually leads to a suppression of the HPA axis (16, 44–48). There are several studies revealing a large interindividual variation in the time for recovery of the HPA axis and no clear correlation between recovery time and dose or length of treatment. However, studies on HPA axis suppression and correlation with psychopathology in patients receiving glucocorticoid therapy are missing. Therefore, we assessed adrenal function before the end of glucocorticoid therapy when suppression of the HPA axis was supposed to be maximal. We found that type 1 patients predominantly scored above cutoff points in the higher range of cortisol and ACTH levels. This leads to the tentative conclusion that a higher, less-suppressible secretion of cortisol and/or ACTH during glucocorticoid therapy is a hallmark of an increased risk of APR. We are aware that this conclusion will

### Table 5. Association between cortisol levels and APR profiles at week 5 in patients with ALL (n = 37)

<table>
<thead>
<tr>
<th>Upper quartile (≥5.0 μg/dL)</th>
<th>Upper tertile (≥4.1 μg/dL)</th>
<th>Group median (1.6 μg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% of type 1 patients (n = 6/20)</td>
<td>40% of type 1 patients (n = 8/20)</td>
<td>60% of type 1 patients (n = 12/20)</td>
</tr>
<tr>
<td>12% of type 2 patients (n = 1/8)</td>
<td>12% of type 2 patients (n = 1/8)</td>
<td>37% of type 2 patients (n = 3/8)</td>
</tr>
<tr>
<td>17% of type 3 patients (n = 1/6)</td>
<td>17% of type 3 patients (n = 1/6)</td>
<td>50% of type 3 patients (n = 3/6)</td>
</tr>
<tr>
<td>0% of type 4 patients (n = 0/3)</td>
<td>0% of type 4 patients (n = 0/3)</td>
<td>33% of type 4 patients (n = 1/3)</td>
</tr>
</tbody>
</table>

### Table 6. Association between ACTH levels and APR profiles at week 5 in patients with ALL (n = 37)

<table>
<thead>
<tr>
<th>Upper quartile (≥12.0 pg/mL)</th>
<th>Upper tertile (≥9.0 pg/mL)</th>
<th>Group median (7.0 pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% of type 1 patients (n = 6/20)</td>
<td>40% of type 1 patients (n = 8/20)</td>
<td>60% of type 1 patients (n = 12/20)</td>
</tr>
<tr>
<td>12% of type 2 patients (n = 1/8)</td>
<td>25% of type 2 patients (n = 2/8)</td>
<td>50% of type 2 patients (n = 4/8)</td>
</tr>
<tr>
<td>17% of type 3 patients (n = 1/6)</td>
<td>17% of type 3 patients (n = 1/6)</td>
<td>50% of type 3 patients (n = 3/6)</td>
</tr>
<tr>
<td>0% of type 4 patients (n = 0/3)</td>
<td>0% of type 4 patients (n = 0/3)</td>
<td>0% of type 4 patients (n = 0/3)</td>
</tr>
</tbody>
</table>
have to be validated on a larger sample size and in a design apt to exclude potential influences by diurnal hormone value fluctuations as well as analytic imprecision (49). Mechanistically, these higher residual endogenous hormone levels may not directly contribute to APR, because they are quantitatively very low compared with the exogenous influx. Rather, a lower propensity to suppression of the HPA axis by exogenous influences may signify a certain pattern of neuroendocrine regulation inclining to APR.

At least in our limited patient cohort, no gross correlation was found between the polymorphisms ER22/23EK, N363S, and Bcl1 and APR. This is in line with earlier findings in which no association was found between these polymorphisms and glucocorticoid sensitivity in ALL cells (28). However, other studies did find a correlation between clinical symptoms of increased glucocorticoid sensitivity (higher body mass index, abdominal obesity, and higher systolic blood pressure) for Bcl1 (18, 26, 27), whereas the clinical relevance of altered glucocorticoid sensitivity of carriers of the mutant ER22/23EK and N363S alleles is not known or controversial. A larger cohort is necessary to exclude potential small clinical differences between subgroups with different mutations.

In spite of their high value in the management of children with ALL and MH, glucocorticoids are not a universal panacea. Continuous efforts to minimize their side effects without jeopardizing outcome are necessary. Our study is the first one to prospectively evaluate APR due to glucocorticoid therapy. Our data implies that the development of APR due to glucocorticoid treatment is measurable by psychological tests and by somatic, in particular, hormonal markers.

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