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Clinical Research

Adherence to Treatment in Children With Epilepsy: Who Follows "Doctor's Orders"?

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Summary: *Purpose:* The goal of the present study was to examine sociocultural, medical, family environment, and individual cognitive factors that predict adherence to treatment in children with epilepsy.

Methods: The study subjects (4–13 years old) were enrolled in a longitudinal seizure study at the first visit to the seizure clinic, attended at least 6 months, and had at least two appointments. Baseline predictors, which were obtained by interview, chart review, and psychometric testing, included sociocultural and family environment, seizure and previous treatment history, child behavior, cognitive functioning (IQ), and family stress. Four latent factors tapping these indicators of risk (acculturative risk, seizure severity, behavior problems, family environment) and two measured variables (IQ and life events) were hypothesized. Outcomes were visit adherence (proportion of scheduled appointments kept, plus proportion without unscheduled contacts), medication report (proportion of visits at which parent report of medication agreed with records), and medication levels (proportion of serum anticonvulsant levels within expected range for dosage). Two-step analytic procedure included confirmatory factor analysis to validate the hypothetical structure of the baseline risk indicators, followed by structural equation modeling to examine longitudinal relations between baseline risk and subsequent adherence outcomes.

Results: Significant prospective relationships included acculturative risk associated positively with visit adherence and medication levels, behavior problems associated negatively with visit adherence and medication levels, family environment associated negatively with medication report, life events associated positively with medication levels and visit adherence, and cognitive functioning (IQ) associated positively with medication levels. Seizure severity was not associated significantly with any adherence outcome. There also were no significant within-time associations between adherence outcomes.

Conclusions: Contrary to clinical expectations, families at higher acculturative risk and with higher life events reported greater adherence. Seizure severity did not influence adherence. The three adherence measures were statistically independent of each other. **Key Words:** Epilepsy—Adherence—Acculturative risk—Life events—Family environment.

Much has been written about the importance of adherence (or compliance) to medical instructions in children and adults with chronic illnesses. Because "compliance" can have negative connotations, many physicians, researchers, and clinicians prefer the term "adherence" to reflect a patient's willingness to follow prescribed medical advice. This article uses "adherence" as an indicator of patient behavior with regard to following medical advice and a physician's instructions.

The problem of adherence to medical advice is not selective but rather is pervasive and affects a broad range of illnesses. Researchers have examined numerous factors as causes and correlates of adherence with the hope of developing effective intervention strategies to improve adherence. Primary among those psychosocial factors hypothesized to influence adherence are access to care (financial and logistical [e.g., distance and inconvenience]) (1), educational (understanding of medical instructions and literacy) (2), cultural factors (language barriers and beliefs about the origin of illness) (3), health beliefs (alternative healing practices and distrust of medical systems) (4,5), patient's assessment of risk of illness and treatment (perceived severity of illness; level of threat; and perceived risks, benefits, and adverse effects of treatment), and complexity of treatment itself (4,6–10). Family psychosocial stress and environment also have been shown to influence adherence and adaptation to chronic illness (11–13).

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A broad array of factors have been examined as part of the overall effort to explain nonadherence, generally with the intent of devising better intervention strategies to improve adherence (14). Research in adherence is methodologically and conceptually problematic, with widely varying approaches applied to measurement and data analysis. In a review of adherence studies, Nichols et al. (15) point out substantial weaknesses and inconsistencies in both utilization of measures and application of analyses. For example, adherence is measured variously by a review of records, patient self-report (16), pill counts (17), prescription refill rates (18), and biological markers, including serum, urine, and salivary assays to quantify medications or their metabolites (16,19). Additional indicators including monitoring of appointment schedules (coming to visits at the provider's convenience, with avoidance of unscheduled calls and visits) assess another unique aspect of adherence (20); however, this assessment approach may not reflect a critical predictor of patient outcomes.

Patient self-report of medication intake is often used, although misperception and underreporting or overreporting can alter results (21). Pill counts are most useful in research settings, where control over medication dispensing by staff provides an objective and accurate means to quantify pharmaceutical adherence. Pill counts are substantially less useful for assessing adherence in a clinic setting, where prescriptions can be filled at a variety of community pharmacies, and patients do not generally bring their medications to visits. In a research setting, medication containers with microprocessors record each time the container is opened, providing a surrogate measure of medication consumption (22–24). Notably, the event recorders may not agree fully with patient report of medication adherence (25).

Predictors of adherence in epilepsy

Improving adherence in patients with epilepsy is particularly challenging to the clinician. Epilepsy is an episodic illness, which requires continuous treatment for good outcome. It is widely assumed that nonadherence is common and a major contributor to poor outcome (26–29). Serum anticonvulsant drug levels are commonly used in epilepsy studies. However, serum anticonvulsant levels, while providing a more objective measure, may be influenced by factors other than adherence, including altered pharmacokinetics resulting from comedication, poor absorption, and genetic differences in drug metabolic rates (30–33). Even in a controlled, institutional setting where adherence is assured, serum anticonvulsant levels vary tremendously (34). In addition, serum levels of several commonly used anticonvulsant drugs are not routinely clinically assessed.

A number of methods have been found to improve adherence to treatment, including the use of educational materials regarding medications, written schedules, or pamphlets (35). Simplification of dosing schedules is associated with improved adherence (36). In the Childrens Hospital Los Angeles (CHLA) Neurology Clinics, all patients routinely received simple written booklets in either English or Spanish about seizures. For each standard anticonvulsant medication, a written information sheet in either English or Spanish was provided outlining expected positive and potential negative effects of the medication, with an emphasis on the importance of taking the medication regularly. A "seizure emergency card" provided a description of what constituted an emergency for a particular patient and gave routine and emergency telephone contact numbers. Complex medication schedules were frequently written out on calendars, particularly if a patient was tapering on or off a medication. Appointment reminders were mailed automatically about 10 days before each visit, and bilingual office staff and translators were available. Physicians attending the epileptic patient also provided detailed medication schedules. A nurse was available to help instruct parents on how to administer medication, including how to use devices such as syringes or tube-spoons for liquids; to crush pills or to use "sprinkle caps."

METHODS

To better understand the psychosocial, behavioral, and medical factors that contribute to adherence, we undertook a longitudinal study of treatment adherence in a select sample of children with epilepsy and their families. The research investigation received approval from the Institutional Review Board of CHLA. Parents provided informed consent for their children, and each child provided an assent to the research procedures.

Subjects

Children with epilepsy between the ages 4 and 13 years were recruited for a longitudinal study of childhood epilepsy at the time of their initial contact with the CHLA Seizure Clinic, regardless of the duration of epilepsy (37). Subjects had at least low-normal cognitive functioning and normal or near-normal motor functioning. Children with moderate or severe mental retardation or significant motor or sensory handicaps, which might interfere with implementation of psychometric tests, were excluded. Subjects also were excluded if the child and parent did not speak either English or Spanish. Informed consent was obtained at the time of the first clinic visit, if the family planned to continue at CHLA. Enrollment continued over a period of 4 years during 1984–1988. For the present study, 119 subjects were included in the analyses based on their having at least 6 months of follow-up data and a minimum of two follow-up visits. Maximum follow-up duration was 30 months.

The CHLA Seizure Clinic serves a diverse population that includes a predominantly low-income, urban, ethnic minority population, with some middle- and upper-income suburban families. This is reflected in the sociodemographic characteristics of the study participants.

Baseline measures

Researchers administered a battery of standardized psychometric tests and self-report questionnaires within 1 month of the child's first visit to the CHLA clinic. Information regarding seizure history, etiology, previous treatments and responses, and other illnesses was abstracted from medical records. In addition to standardized assessments, the investigative team developed several brief questionnaires to provide supplementary information on acculturative risk. A bilingual member of the research staff administered questionnaires to the parents in the family's preferred language. Mothers were generally the primary respondent, unless the child routinely came to the clinic with another family member.

The individual measures of medical, behavioral, and psychosocial data were grouped conceptually into four risk domains: acculturative risk, seizure severity, behavioral problems, and family environment. Two additional measures assessed cognitive functioning as determined by intelligence quotient (IQ) and life events. The availability of multiple indicators (items) used to assess each conceptual domain makes it possible to hypothesize latent constructs with the use of confirmatory factor analysis (CFA) methods. This analytic approach stands in contrast to more exploratory factor analytic methods that rely on subjective interpretation and do not provide objective statistical criteria to evaluate empirical findings. With CFA procedures, a researcher can specify a priori a hypothetical model and test the statistical fit of this model against the sample covariances. Moreover, nested model strategies permit statistical evaluation of the fit of alternative and more parsimonious model specifications. Specification of a hypothesized model structure consists of constraining certain items (indicators of risk) to load in a particular fashion on one or more latent constructs. Latent constructs are statistical abstractions hypothesized to "cause" the covariation among the indicators. Usually, the hypothetical structure includes one nonzero loading for each indicator on a latent construct (thus mimicking a simple structure). Model fit is then determined statistically by evaluating the correspondence between the implied population model and the sample covariances (against a null model that specifies no a priori factor structure).

To illustrate this methodological approach and acculturative risk used as an example, the moderate associations among the four indicators tapping education, nativity, nationality, and primary language reflect distance from the dominant culture. Each indicator (observed measure) captures a slightly different aspect of acculturative risk, however, there also is some modest overlap among the indicators. The conceptual and empirical overlap provides a basis to posit (hypothesize) a latent construct of acculturative risk. Within each of the hypothesized risk domains, initial exploratory analyses helped to eliminate nonessential measures that did not adequately reflect the four dimensions (item and scale selection was based in part on tests of factorial validity with the use of exploratory methods and criterion validity based on predictive relations with target outcomes). The CFA provides two essential pieces of information that detail the psychometric soundness of the hypothesized model and the statistical relations among the model components (constructs and observed measures). First, the CFA provides estimates of how strongly each indicator reflects the latent construct (i.e., standardized factor loadings). Based on classic psychometric theory, variance reflected in the factor loading is disaggregated from measurement error and thus represents a "true" indicator of the latent construct. A second component, the residual variance for each indicator (non–factor-determined component of variance), reflects unique or test-specific individual differences net of prediction from the factor.

A second piece of information from the CFA model details the statistical associations (i.e., intercorrelations) between the several risk domains and individual indices of risk (i.e., life events and IQ). Although the latent constructs that tap medical, behavioral, and psychosocial risk reflect essentially different facets of risk, there is to be expected a moderate level of overlap that can point toward clinically meaningful profiles. Statistical model fit indices for the CFA (as well as the longitudinal structural model) include determination of how well the sample data fit the hypothesized model structure. These and other fit indices are described in greater detail after the presentation of each model. More detailed explanations of the psychometric and statistical theory underlying CFA methods are available elsewhere (38,39).

Acculturative risk

Four items were used to reflect a latent construct of acculturative risk. Mother's education was used to assess socioeconomic resources, whereas nativity of parents (primarily mother, recorded as length of residence in the United States), child's nationality, and primary language all reflected distance from the dominant culture. Additional measures available from the questionnaires included income, public assistance, method of transportation to clinic, and single- versus two-parent household. However, in analyses not shown here, these measures did not provide unique predictive information and did not contribute to the statistical reliability of a latent factor of acculturative risk. The distributions for maternal educa-

tion and years in the United States were skewed and non-normal; thus, these items were transformed into categorical measures (ranging from 1 to 3). Higher acculturative risk scores indicate greater distance from the dominant culture in terms of nativity, socioeconomic power, and language use at home.

Seizure severity

Four indicators reflected a latent construct of seizure severity: type or types of seizure and current and maximum seizure frequency, age of onset, duration of the seizure disorder, and prior treatment (successful versus unsuccessful, number of medications used in the past, and reasons for previous medication changes). All four indicators were based on information obtained from the parent by the examining physician or were extracted from available medical records. Higher scores on this construct reflect more frequent or severe seizures, earlier onset of epilepsy, longer history of ongoing seizures, and more frequent problems with previous treatments.

Behavior problems

Three indicators reflected a latent construct of behavior problems. Research staff developed the Childrens' Hospital Behavior Questionnaire (CHBQ) to assess the parent's perception of the child's attention span, behavior, and activity level. The CHBQ is available in both English and Spanish. Previous research in studies of anticonvulsant medications with epileptic children demonstrated the reliability and validity of the CHBQ (40). High scores on this construct reflect a combination of poor attention span, lack of behavioral control, and high activity levels that cumulatively indicate heightened risk.

Family environment

Four subscales of the Moos Family Environment Scale (FES) reflected a latent construct of family environment. The four subscales included cohesion, organization, independence, and conflict. Extensive information is available regarding the reliability and validity of the FES with a wide array of clinical and nonclinical populations (41,42). Overall, high scores on this latent construct reflect a positive, coherent, and organized family environment with low levels of reported conflict.

Development/cognitive

Depending on age at enrollment and primary language, IQ was measured with either the McCarthy Scale of Children's Abilities (43), the Wechsler Intelligence Scale for Children–Revised (WISC-R) (44), or the Spanish version of the WISC-R, the Escala Inteligencia por Ninos Wechsler (EINW-R) (45). The McCarthy General Cognitive Index (GCI), the WISC-R, and EINW-R Full Scale IQ, although not identical, are closely related in their ability to tap cognitive functioning (43). Because the standard deviations vary slightly between these psychometric instruments, IQ was converted to standardized scores for analysis.

Stressful life events

The Coddington Life Events Scale for Children (LES) provided an assessment of life stresses experienced by the family during the year before enrollment (46). Normative data for the LES include both weighted and unweighted (counts of total number of events) scoring methods. For the present analyses, unweighted scores were used, because normative published data relied on weights from a demographically different population. Overall, we hypothesized that a high LES score and low cognitive functioning contribute to poor adherence.

Outcome measures

Assessment of outcome included three different facets of adherence. Information was recorded for each scheduled appointment, regardless of whether the appointment was kept. Information included whether the family came on the scheduled date, reported medication adherence by the parent (as recorded by the clinician seeing the child), and medication adherence determined by the physician based on serum anticonvulsant levels. In addition, each family was queried and medical charts were reviewed to assess unscheduled visits or telephone requests for medication refills, emergency department visits, and visits elsewhere for seizure management. We combined this information into three (observed) indicators of adherence. Visit adherence was used to assess the sum of the proportion of scheduled appointments that were kept plus the proportion of visits without intervening unscheduled contacts. Medication adherence by parent report included the proportion of visits at which parent report of medication administration was concordant with medical prescription. Medication adherence by serum anticonvulsant level was used to assess the proportion of serum anticonvulsant levels judged by a physician to be appropriate for prescribed dosages. Computation of adherence measures relied on varying denominators. For visit adherence, denominator was number of appointments, and the potential range was 0–2. For medication adherence by self-report, the denominator was the number of total visits and ranged from 0 to 1. For adherence by medication levels, the denominator was the number of serum levels measured and ranged from 0 to 1.

Data analysis and modeling strategies

The EQS statistical program was used to conduct the confirmatory modeling procedures and test the longitudinal path model (47). As previously described, the CFA portion of the analysis provides information regarding the psychometric soundness of the hypothesized model as well as an opportunity to inspect the intercorrelations among the various indices and latent constructs of risk. A second step in the analytic procedure involved testing the

longitudinal portion of the model using structural equation modeling (SEM). SEM provides a rigorous means to evaluate the multivariate influences of risk on adherence without inflating the experiment-wise error rate. The CFA model remains intact in the SEM model and permits a more rigorous examination of the effects of risk on later adherence with all of the observed measures corrected (adjusted) for measurement error. For the longitudinal model, the various adherence outcome measures were regressed simultaneously on the baseline risk factors and measured indicators. Statistical information from the SEM model indicates the unique influence of each domain risk on later adherence (i.e., partial effects controlling for each individual risk domain). Additional features of the SEM include estimation of the magnitude of cross-sectional associations among the baseline predictors and specification of the magnitude of relations among the adherence outcomes (net of prediction). More didactic and comprehensive explanations regarding the application of SEM in clinical research are provided elsewhere (38,48,49).

RESULTS

One hundred nineteen subjects (43% boys and 57% girls, age 3.9–13.9 years, median age 8.3 years) were available for analysis. Descriptive statistics for baseline predictors and outcome measures are given in Table 1. Several continuous variables were converted to categorical variables. After conversion, there are no significant deviations from normality. The far, right-hand column presents point-biserial correlations between each observed measure and gender. When squared, these terms represent the amount of variance accounted for by gender (and are a useful indicator of mean differences based on gender). Overall, gender accounts for only a small

TABLE 1. *Summary descriptive statistics for measures used in the model*

Latent construct and measured variables	Mean	SD	Range	Mean difference by gender r_{pbi}
Baseline assessment				
Acculturative risk				
Maternal education[a]	2.08	0.68	1–3	−0.07
Primary language[b]	0.39	0.49	0–1	0.08
Mother's years in US[c]	0.24	0.43	0–1	0.01
Child's nationality[d]	0.17	0.38	0–1	−0.02
Seizure severity				
Maximum frequency[e]	0.59	0.49	0–1	−0.01
Seizure duration[f]	2.10	0.91	1–3	0.15
Age at first seizure[g]	2.15	0.78	1–3	−0.10
Prior treatment failure[h]	0.72	0.77	0–2	0.02
Behavior problems				
Activity	2.27	1.83	0–7	0.04
Attention	2.45	1.84	0–7	0.11
Discipline	2.37	1.73	0–5	0.01
Family environment scale				
FES cohesion	7.22	1.73	1–9	−0.05
FES organization	6.37	2.11	1–9	0.03
FES conflict	2.86	1.90	0–8	0.01
FES independence	6.29	1.44	3–9	−0.10
IQ (WISC-R FSIQ, GCI)	90.48	18.23	49–129	−0.08
Life events	5.08	2.61	0–12	0.02
Adherence measures				
Visit adherence	1.52	0.36	0.17–2	0.04
Medication by parent report	0.88	0.19	0–1	−0.03
Medication by blood levels	0.86	0.28	0–1	−0.10

The following continuous variables were converted to categorical variables due to markedly skewed distributions or outliers: maternal education, mother's years of residence in the US, maximum seizure frequency, duration of seizure disorder, and age at first seizure.

[a] 1, <6 yr; 2, 6–11 yr; 3, ≥12 yr.

[b] 0, English; 1, other.

[c] 0, ≥10 yr or U.S. native born; 1, <10 yr.

[d] 0, U.S. native born; 1, immigrant.

[e] 0, new onset; <1 convulsive seizure/mo or <1 nonconvulsive seizure/wk 1, ≥1 convulsive seizure/mo or 1 nonconvulsive seizure/wk.

[f] 1, <1 mo; 2, 1 mo to 1 yr; 3, >1 yr.

[g] 1, birth to 3 yr; 2, 3 to 6 yr; 3, >6 yr.

[h] Three variables were dichotomized (1, risk; 0, no risk) and combined to form a unit-weighted risk index of prior treatment failure (one point each): >6 mo between first treatment and seizure control; any anticonvulsant stopped; any episode of anticonvulsant intoxication.

proportion of the variance, and there were no significant differences in levels of risk or adherence based on gender. Given the lack of substantive differences based on gender and the small sample size, we combined males and females for all subsequent analyses.

Forty-five percent of families identified languages other than English, most commonly Spanish, as the primary language spoken in the home. Korean, Chinese, and Armenian speakers were represented as well. Thirty-nine percent of the children spoke a language other than English as their preferred language (all Spanish). Maternal education also reflects the diversity of the subjects, ranging from no formal education through postgraduate degrees. Immigrant parents from Central America and Mexico generally completed fewer than 6 years of formal education.

Figure 1 shows the results of the CFA measurement model. Rectangles are used to designate the measured variables (observed indicators), whereas large circles represent latent factors (hypothesized dimensions of risk). Numbers on the single-headed arrows that point to the rectangles are standardized factor loadings and depict the magnitude or strength of each respective measure as an overall indicator of the latent construct. Small circles with numbers inside denote residual variances and represent the unique measurement component that is not determined by the common factor (a combination of error and test-specific variability). Consistent with conventional regression notation, squaring these residual variances and subtracting them from one indicates the amount of variability in each measured indicator net of prediction from the factor. Smaller residual variances indicate greater reliability for the latent factor. Model fit indices showed the fit of this model to be adequate: χ^2 (139, N = 119) = 215.4, $p < 0.001$, Comparative Fit Index (CFI) = 0.864. The relatively large magnitude of each loading and their statistical significance ($p < 0.001$) underscore the psychometric soundness of the hypothesized model and reinforce that we have correctly hypothesized a statistically reliable latent structure. Furthermore, as a goodness-of-fit index, the CFI (which ranges from 0, indicating a poorly fitted model, to 1, indicating a perfect model fit) closely approximates the benchmark criteria of 0.90 and reinforces there was little discrepancy between the implied population model and the sample covariances. Associations among the baseline predictors are not depicted but are described along with the structural portion of the analyses.

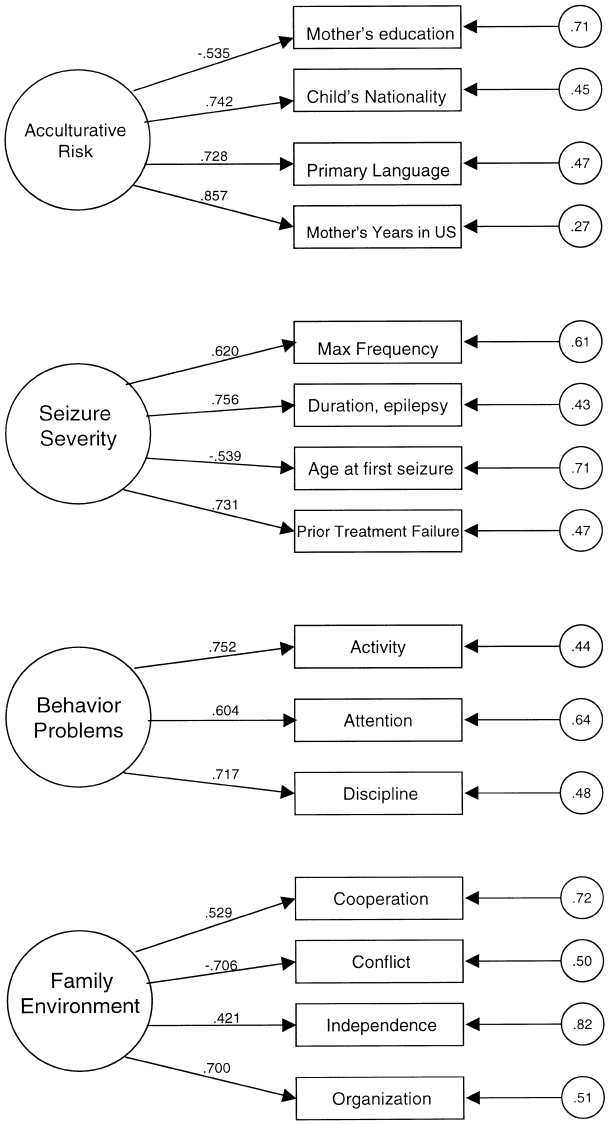

FIG. 1. Confirmatory factor analysis model. Large circles designate latent factors; rectangles are measured (observed) variables. Numbers on arrows represent standardized factor loadings indicating the statistical reliability of the measure as an indicator of the factor. Numbers in the small circles represent residual variances (variability in the observed measure not explained by the factor). All loadings are significant at $p < 0.001$. Significance levels were determined by critical z-ratio of unstandardized coefficient divided by its standard error.

Results of the longitudinal structural model analysis

The next step in the analyses combined the results of the CFA model with a test of the longitudinal relations between baseline assessments of risk and adherence outcomes. The structural equation model assesses the long-term effects of risk on adherence within a multivariate framework and is often termed a causal or path regression model. In essence, each of the baseline risk assessments is hypothesized to statistically cause the adherence outcomes and model parameters detail the magnitude of these effects. One essential difference in model construction between the CFA and SEM is the replacement of correlations between baseline predictors and adherence outcomes in the CFA analysis with across-time (i.e., causal) regression paths in the SEM. The SEM also includes specification of correlations among the baseline predictors. Consistent with conventional regression ap-

proaches, the prediction of each adherence outcome produces a residual term (disturbance) that reflects variation net after prediction. The SEM also specified correlations among these residual disturbances. Inferring causal relations among the baseline predictors of risk and likewise among the adherence outcomes (both of which reflect contemporaneous associations) would be regarded at best as tenuous.

Figure 2 shows the results of the final SEM. Among the long-term relations, acculturative risk was associated positively and significantly with visit adherence and medication levels. The factor behavior problems was associated negatively and significantly with visit adherence and medication adherence (by serum levels). Family environment was associated negatively and significantly with medication adherence by parent report. A measure of life events was associated positively and significantly with medication levels and visit adherence. Cognitive functioning (IQ) was associated positively and significantly only with medication levels. Interestingly, seizure severity was not associated significantly with any of the adherence outcomes.

Associations among baseline risk assessments

Many of the baseline latent factors and measured variables (IQ and life events) also were associated significantly. These associations reflect heightened levels of risk that through their combined influence portend less patient adherence. For instance, although seizure severity did not predict any of the adherence outcomes, it was associated significantly and positively with life events ($r = 0.22$, $p < 0.05$) and behavior problems ($r = 0.23$, $p < 0.05$) and negatively with IQ ($r = -0.18$, $p < 0.05$) and acculturative risk ($r = -0.35$, $p < 0.01$). Acculturative risk was associated negatively and significantly with IQ ($r = -0.22$, $p < 0.001$), life events ($r = -0.25$, $p < 0.01$), and seizure severity ($r = -0.35$, $p < 0.01$) and positively with family environment ($r = 0.21$, $p < 0.05$).

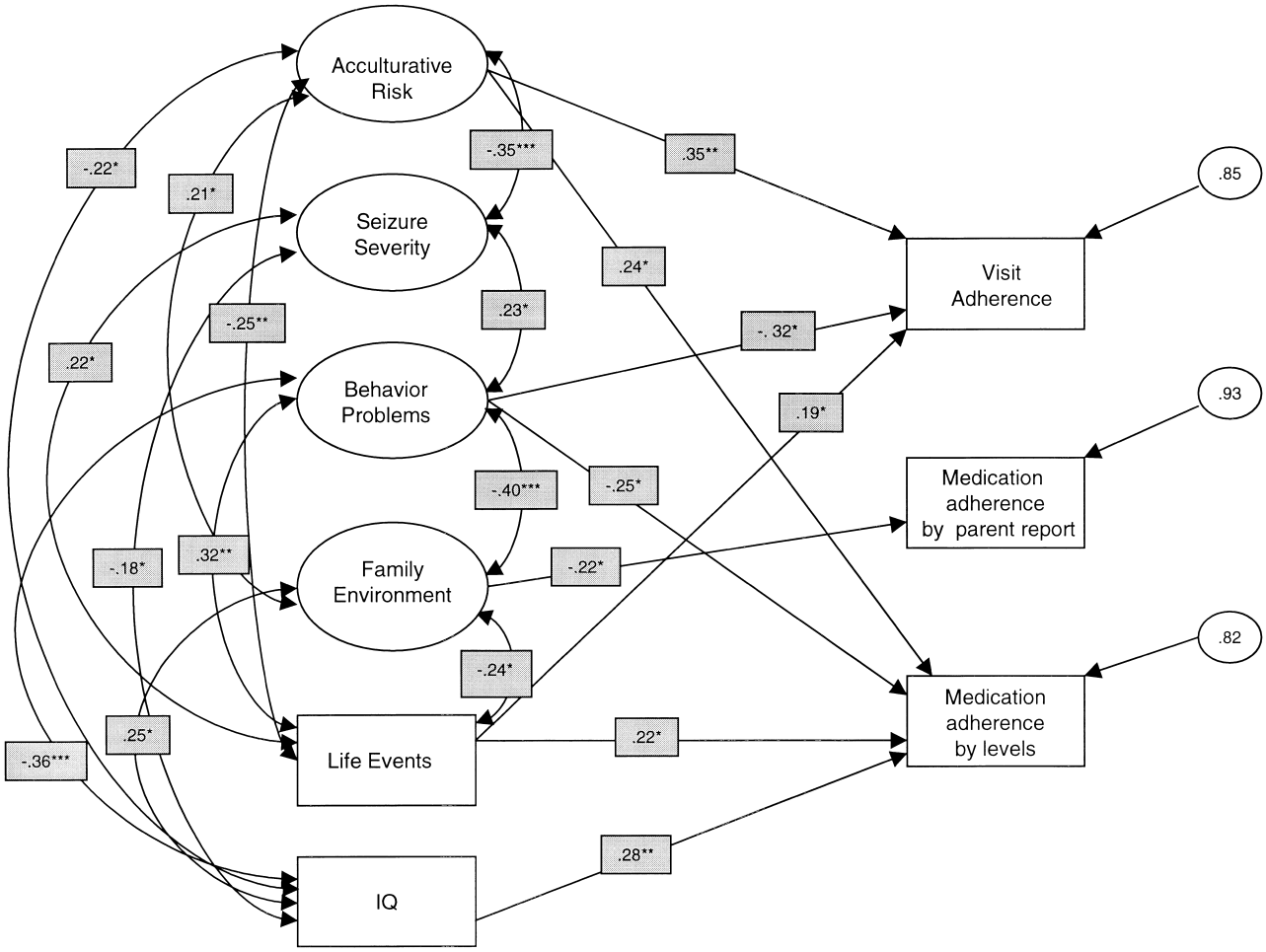

FIG. 2. Results of the longitudinal structural equation model. Left side depicts baseline assessments including latent factors (circles) and free-standing variables (rectangles). Right side designates adherence outcome measures. Solid lines indicate statistically significant paths. Numbers on the lines represent partial standardized regression coefficients, representing the unique contribution of the predictor to the outcome. Numbers in the small circles represent residual variances. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. IQ represents either full-scale IQ (WISC-R or EINW-R) or McCarthy GCI (z transformed).

Behavior problems was associated significantly and negatively with IQ ($r = -0.36$, $p < 0.001$) and family environment ($r = -0.40$, $p < 0.001$) and positively with life events ($r = 0.32$, $p < 0.01$). Family environment was associated significantly and positively with IQ ($r = 0.25$, $p < 0.05$) and negatively with life events ($r = -0.24$, $p < 0.05$). Interestingly, there were no statistically significant associations among the outcome measures of adherence.

The final model trimmed of nonsignificant paths and associations fit well: χ^2 (139, N = 119) = 215.4, $p < 0.001$, CFI = 0.864. The ratio of χ^2 to *df* of 1.54 indicates a good fit between the sample covariances and implied population model, and the CFI indicates that 86% of the sample covariation is accounted for by the hypothesized model. Despite falling slightly under the benchmark of 0.90, enhancement of this fit index with the addition of residual covariances (unique associations among the baseline indicators of risk) or nonstandard effects (paths from residual terms associated with baseline predictors to later outcomes) might capitalize on chance given the small sample size and not replicate well (50,51).

DISCUSSION:

Adherence poses difficult issues for all clinicians and special problems for those involved in the treatment of childhood epilepsy. First, no single measure represents a completely valid indicator of risk for nonadherence. To remedy this, the present study included a wide range of factors likely to reflect risk and vulnerability to poor adherence. An important strength associated with the present study is a reliance on multiple indicators of risk and the application of confirmatory techniques. Importantly, results from the CFA model indicated that risk is multidimensional and includes related but somewhat distinct facets of sociocultural, medical, behavioral, environmental (i.e., family), and individual characteristics. Results of the structural equation modeling indicated that the most efficient of these risk factors turned out to reflect sociocultural and behavioral vulnerability as opposed to information pertaining to medical or seizure history. Likewise, a similar concern applies to measures of adherence used broadly. Individually, few measures of adherence paint a complete picture of the factors associated with following doctors' orders. None of the outcome measures used in the present study represent ideal barometers of patients' willingness to adhere to treatment recommendations or are likely to reflect a complete picture of adherence to therapy when used alone. However, in combination, multiple measures of adherence provide a more complete picture of the many factors associated with the medical, psychological, and psychosocial motivations to comply with physicians' instructions.

In a related vein, the best measure of adherence is not always obvious, as exemplified by family report of medication intake. Such a measure is rarely fully accurate, if independently verified by pill counts or mechanical devices, such as pill containers that record opening times. Because many of the parents in our study were of limited literacy, we opted for a liberal definition of adherence by family report. We rated the participating families adherent if they reported giving the proper quantity and appropriate medicine description, even if they could not name the medication or report the dosage in milligrams. For example, a parent stating "I give two of the round white pills twice a day" was considered adherent if the prescription in the chart was 400 mg of generic carbamazepine twice a day.

Anticonvulsant drug serum levels may provide a measure of adherence, but various factors can influence these measures, including genetic differences in drug metabolism, concomitant medications, food, time of day, and other factors. In the present study, only serum levels viewed by the clinician as extremely low for the prescribed dose were rated as nonadherent. Unexpectedly high levels (rarely found) were not rated as nonadherent, despite the possibility that parents or patients may have increased the medication dosage without physician direction.

This study found little support for several common prejudices and beliefs regarding patient adherence. Contrary to our expectations, families reporting less parental education, who were non-English speaking, who had a lower income, and who were recent immigrants were more likely to keep appointments and avoid unscheduled contacts with physicians or medical staff. This relation was one of the strongest relative effects in the model. In contrast, seizure frequency, duration, and previous treatment failures, usually thought to be valid prognostic indicators of later adherence, did not contribute to treatment adherence. In effect, adherence was equally likely in the face of long-standing refractory or severe epilepsy or new-onset epilepsy with only a few reported seizures. Behavioral comorbidity lowered both medication and visit adherence. Overall, this effect was relatively strong, particularly on visit adherence. We speculate that parents with the additional stress of managing a child who they perceive as overactive, inattentive, or uncooperative may have substantially more difficulty attending visits on schedule. Contrary to expectations, patient families reporting high levels of stressful life events were more likely to adhere to treatment. One explanation for this relation suggests that families reporting higher levels of stress used medical guidance and contact with physicians as an instrumental coping mechanism.

In addition to acknowledging the independent influence of each risk factor on later adherence, the moderate associations among the baseline predictors also should

be noted. Seizure severity had no long-term influence on later adherence but was moderately associated with three of the baseline factors. In effect, seizure severity may not play an independent role in determining adherence but may play an integral role in shaping vulnerability through behavioral and family systems. In our sample, higher acculturative risk was associated with lower seizure severity scores, probably due to referral patterns. Higher-income, nonminority families were more likely to have been referred after beginning treatment elsewhere, or for a "second opinion," whereas minority, low-income families were more likely to begin treatment in our clinic or in the emergency department of CHLA. This differential selection mechanism may influence adherence indirectly, because referred patients may have included an excess of both medically more difficult and less adherent patients. The very strong relationship between acculturative risk and adherence also may obscure the possible effects of seizure severity, due to the negative correlation of the two factors at baseline.

The three adherence measures had surprisingly little statistical overlap. Families who kept appointments were no more likely to have appropriate anticonvulsant levels than were those who did not keep appointments. Similarly, parental report of medication adherence was only minimally correlated with adherence judged by serum levels. Given the statistically independent effects of the several baseline risk predictors to each adherence outcome, these findings underscore the importance of using multiple adherence measures to capture the full spectrum of clinically meaningful indicators.

Our results differ from those of Pachter and Weller (3), who examined the effect of acculturation on adherence to asthma therapy among Puerto Rican families residing in Philadelphia. Asthma and its treatment often have been compared with epilepsy and its treatment: because both represent episodic conditions that generally require continuous therapy, even during periods without symptoms. Pachter and Weller used serum theophylline levels as a measure of adherence, analogous to our use of serum anticonvulsant drug levels, and found that more acculturated families were more likely to comply with therapy.

Non-adherence to therapy may be intentional on the part of parents and patients or unintentional due to forgetfulness, misunderstood directions, child-care arrangements not conducive to administration of medications, busy parents, and complex medication schedules. Families may intentionally not adhere to treatment recommendations if they do not trust the physician or the health care system; are fearful of "addiction," oversedation, or behavior problems due to medication; or seek nonmedical alternative treatment of their child's epilepsy. At times, nonadherence may be due to rational, well thought-out concerns, which were, however, not discussed with the physician (52). Although we did not examine additional perceived reasons for nonadherence in this study, the finding that higher socioeconomic status was associated with greater adherence difficulties suggests that at least in some instances, nonadherence was intentional, not due to difficulties in access to care or understanding of directions. Nonadherent parents may also feel less dependent on the physician because they have other resources, including the ability to consult multiple physicians.

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