The impact of paediatric inflammatory bowel disease. Epidemiology, disease activity and quality of life

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Chapter 2.1

Assessing Activity of Paediatric Crohn's Disease: Which Index to Use?

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Abstract

Background & Aims

The Paediatric Crohn's Disease Activity Index (PCDAI) is a multi-item measure that, in contrast to the adult-derived CDAI, includes linear growth and places less emphasis on subjectively reported symptoms but more on laboratory parameters of intestinal inflammation. This study compared the feasibility, validity, and responsiveness of PCDAI vs. CDAI in the assessment of Crohn's disease activity among paediatric patients.

Methods

Eighty-one children and adolescents with Crohn's disease were studied. A gastroenterologist provided a categorical global assessment of disease activity as quiescent, mild, moderate, or severe after interview and physical examination. CDAI and PCDAI scores were calculated by an independent appraiser.

Results

Mean values within each category for CDAI and PCDAI differed significantly between strata. PCDAI values were quiescent, 6.8 +/- 6.6; mild, 18.7 +/- 7.3; moderate, 38.5 +/- 12.9; and severe, 54.2 +/- 14.0. CDAI values were quiescent, 23.5 +/- 53.6; mild, 96.0 +/- 60.7; moderate, 184.5 +/- 97.0; and severe, 284.4 +/- 85.8. Individual scores showed less overlap between strata for PCDAI than for CDAI. PCDAI showed better correlation with serum orosomucoid and platelet count, laboratory parameters of inflammation not included in either index.

Conclusions

Both PCDAI and CDAI reflect disease activity in paediatric Crohn's disease. PCDAI is better at discriminating between levels of disease activity.

Introduction

No single clinical or laboratory parameter always accurately reflects activity of intestinal inflammation in Crohn's disease (CD).[1] Hence, multi-item measures of disease activity have been developed for use in clinical trials.[2-4] The widely used Crohn's Disease Activity Index (CDAI) was developed for use in adult patients.[2] However, the CDAI does not consider aspects of CD unique to children, most notably the potential for linear growth impairment as a manifestation of active disease. The Paediatric Crohn's Disease Activity Index (PCDAI) was developed and validated as an evaluative multi-item index for use in multicenter trials among children and adolescents.[5,6] There is considerable overlap with the domains of the CDAI. The differences can be summarised as follows: the PCDAI discarded use of anti-diarrhoeal agents; decreased the weighting of subjectively reported abdominal pain, general well being, and diarrhoea; increased the number of laboratory parameters; and added linear growth.

Clinical experience has suggested that the CDAI may under represent disease activity among paediatric patients[7] because of the heavy weighting on subjective reporting of symptoms and the tendency for many children and teenagers to minimize somatic complaints. Nevertheless, the CDAI is still used as the primary outcome variable in paediatric trials despite its lack of validation in paediatric populations and recognized difficulties in both feasibility and reproducibility even among adult patients with CD. We compared the PCDAI with the CDAI in the assessment of intestinal inflammatory activity in children and adolescents with CD. The aim was to provide data on feasibility, validity, significance of scores, and responsiveness that will guide investigators in the selection of a multi-item measure for future clinical trials in paediatric CD.

Materials and Methods

Between May 1997 and August 1997, children and adolescents younger than 18 years attending The Hospital for Sick Children for assessment of CD were asked to complete a 7-day diary to facilitate computation of the CDAI. [2] The diagnosis of CD was established in all patients according to conventional radiological, endoscopic, and histological criteria. The diary and an explanatory letter were mailed to families 1 week before their appointment. If patients did not receive the diary or forgot to complete it, they were asked to fill out the diary retrospectively.

At the hospital visit, each patient was interviewed by the attending paediatric gastroenterologist (AMG or PMS) who provided a global assessment of disease activity as quiescent, mild, moderate, or severe on the basis of history and physical examination. Height and weight were measured and plotted on the standard growth charts of Tanner et al.[8]

The research assistant (HL) recorded patient demographic data and laboratory parameters. These included those required for calculation of the CDAI (hematocrit) and PCDAI (hematocrit, serum albumin, and erythrocyte sedimentation rate [ESR]), as well as serum orosomucoid and platelet count. Two versions of the CDAI were calculated for all patients: an original version 2 and one previously modified for use in paediatric patients.[7] In the modified CDAI, "use of opiates or Lomotil for diarrhoea" is replaced by "number of days unable to go to school or participate in normal activities because of CD". The concept of "standard weight" is not applicable to growing children and is therefore replaced by "the ideal weight for height" as determined from the growth curves of Tanner et al.[8] An additional measure of disease activity, the Harvey-Bradshaw index (HBI),[4] as modified by Myren et al.,[9] was calculated for all patients.

To assess the ability of the CDAI and PCDAI to detect a change in clinical status, patients attending the inflammatory bowel disease clinic for a second visit during the period of study had all assessments repeated. Disease activity was categorized as the same, somewhat improved, much improved, somewhat worse, or much worse, according to change in physician global assessment.

The study was approved by The Hospital for Sick Children Research Ethics Board.

Statistical Analysis

All statistical analyses were performed using SAS (SAS Institute, Cary, NC).[10] Results are expressed as means $\pm$ SD. Mean CDAI (original and modified) and PCDAI for the initial patient visit were calculated for all patients. Box-and-whisker plots were generated to show the distribution of PCDAI and CDAI scores within each category of disease severity, as assigned by physician global assessment. Analysis of variance (ANOVA) was used to compare means for each index across the four levels of global assessment. Pearson coefficients were used to assess correlation between CDAI and PCDAI scores, the Harvey–Bradshaw scores, and individual laboratory parameters of disease activity. Because the physician global assessment is an ordinal variable, these analyses were also performed using Spearman rank coefficients. PCDAI and CDAI were analysed as the independent variables in a linear regression model to assess how well each was predictive of the physician global assessment. Because of the ordinal nature of the physician global assessment, ordinal logistic regression was applied to assess the predictability of the indices on global assessment. To compare the responsiveness over time of the two measures, we determined the correlation between the change in PCDAI scores against the change in CDAI scores for patients having a second visit during the study period.

Results

The clinical characteristics of the 81 children and adolescents included in the study are summarised in Table 1. Four patients were evaluated at the time of their initial diagnosis of CD. Twenty-seven of 81 patients (35%) forgot to bring the diary card to the hospital visit or had failed to complete it as instructed, necessitating completion by recall or completion prospecti-vely from the time of the clinic visit. Based on physician global assessment, 36 patients had quiescent CD at the time of evaluation. Activity of CD was judged to be mild in 19 patients, moderate in 20, and severe in 6.

Table 1.
Patient Characteristics at Baseline.

Total number of subjects	81
Sex (M/F) [a]	48 (59.3)/ 33 (40.7)
Age (yr) [b]	14.1 ± 2.4
Age range (yr)	5.1–18.0
Disease distribution [a]	
Small bowel only	28 (34.6)
Small and large bowel	41 (50.6)
Large bowel only	12 (14.8)
Previous surgery [a]	14 (18.2)

[a] Values are expressed as n with the percentage in parentheses.
[b] Values are expressed as mean +/- SD.

The modified CDAI correlated very closely with the original CDAI (r= 0.98), and further comparisons with the PCDAI and with laboratory parameters are therefore reported for the original CDAI alone. As shown in Table 2, correlations between the CDAI, PCDAI, physician global assessment, and HBI were excellent. However, the PCDAI showed a better correlation with laboratory parameters of intestinal inflammation, including serum orosomucoid, which does not factor in the PCDAI scale. Because hematocrit, ESR, and serum albumin are included in the calculation of the PCDAI and hematocrit alone in the CDAI, correlation coefficients with each individual laboratory parameter were recalculated with the specific laboratory parameter contribution removed from the index. The three correlation coefficients of the three revised PCDAIs (PCDAI without hematocrit, PCDAI without ESR, and PCDAI without albumin) with hematocrit, ESR, and albumin predictably lessened but still remained significant. The correlation coefficient between the revised CDAI (CDAI without hematocrit) and hematocrit was no longer significant. The results obtained using Spearman rank coefficients yielded similar results and are not reported.

Prediction of physician global assessment was more reliable for the PCDAI (R^2= 0.75) than the original CDAI (R^2= 0.59) by regression analysis. When both indices were analysed simultaneously, the CDAI did not add to the predictiveness of the PCDAI model (R^2= 0.75).

CDAI and PCDAI values within each stratum of disease activity (determined by physician global assessment) are shown in box-and-whisker plots in Figures 1 and 2. The mean values for CDAI and PCDAI differed significantly between strata (F= 37.4 and p= 0.0001 for original CDAI; F= 76.4 and p= 0.0001 for PCDAI). However, as shown in Figures 1 and 2, there was less overlap for PCDAI scores between patients in different categories of disease activity. When the previously determined cut scores for the two indices were used, there were a greater number of misclassified subjects with the CDAI than the PCDAI. Roughly 80% of children judged to have mild disease and 35% of those judged to have moderate disease had CDAI values of < 150, scores indicative of inactive disease in adults (Figure 2).[2] Children judged by the physician to have mild or moderate disease activity, who were misclassified by the CDAI, had a significantly ($p< 0.0001$) lower mean value for the subjective symptom diary component (69.5 $\pm$ 45.1) than those in the same global assessment category who were correctly classified by the CDAI (192.3 $\pm$ 82.9). When the results were compared for patients who completed the CDAI diary prospectively with those who completed it by recall, no significant difference was noted in the percentage of misclassified patients (data not shown).

Table 2.

Correlations Between Indices and Laboratory Parameters.

	PCDAI	Original CDAI	Modified CDAI	Harvey–Bradshaw
Global assessment	0.86	0.77	0.76	0.72
PCDAI		0.86	0.86	0.84
Original CDAI			0.98	0.91
Modified CDAI				0.93
Harvey–Bradshaw				

	ESR	Orosomucoid	Albumin	Platelet count	Hematocrit
Global assessment	0.50	0.54	-0.60	0.37	-0.37
PCDAI	0.58	0.57	-0.68	0.24	-0.41
Original CDAI	0.45	0.34	-0.60	0.15 [a]	-0.40
Modified CDAI	0.40	0.32	-0.54	0.10 [b]	-0.30
Harvey–Bradshaw	0.41	0.40	-0.46	0.02 [c]	-0.26

[a] p= 0.200.
[b] p= 0.394.
[c] p= 0.849; for all other values, $p< 0.05$.

Using physician global assessment of disease activity as the gold standard, Hyams et al.[5] determined cut scores for the PCDAI, which correctly classified the greatest number of patients: $\leq$ 10 for inactive disease, 11–30 for mild disease, and > 30 for moderate/severe disease. In the present study, again using the physician global assessment as the gold standard, 27 (75%) of 36 patients with quiescent disease, 13 (72%) of 18 patients with mild disease, and 20 (83%) of 24 children with moderate or severe disease were correctly classified by the previously recommended PCDAI cut scores. Focusing on the discrimination between quiescent and mild disease and using the data from our study, a receiver operating

characteristic curve was calculated to select a cut score that would provide optimal sensitivity and specificity. The previously recommended cut score of ≤ 10 gave a sensitivity of 75% and a specificity of 90.5%.[5] The best discrimination occurred with a cut score of < 15, whereby the sensitivity increased to 83% even though the specificity remained unchanged at 90.5%.

Seventeen patients were reviewed at a second visit. PCDAI and CDAI were similar in reflecting change over the short term. The correlation between the adult CDAI difference scores and PCDAI difference scores was strong ($r= 0.92$; $p< 0.0001$).

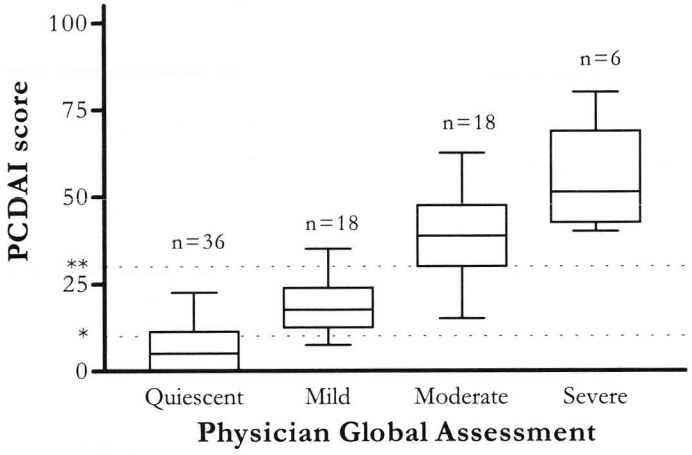

Figure 1.

Box-and-whisker plot of PCDAI scores among patients categorized by physician global assessment of disease activity. The box shows the 25th percentile, median, and 75th percentile. The whiskers show the range of the data. The PCDAI score could not be calculated (laboratory value missing) for 3 patients (1 mild, 2 moderate).
* Cut score for inactive disease (≤ 10).[5]
** Cut score for moderate/severe disease (> 30).[5]

Discussion

The choice of a multi-item measure for use as a primary outcome variable in clinical trials should be based on evidence of its feasibility, reliability, validity, and responsiveness.[11] When the PCDAI was originally validated,[5] PCDAI scores were compared with physician global assessment and with the HBI but not with the CDAI, the instrument most often used to quantitate disease activity. The results of the current study support the preferential use of the PCDAI vs the CDAI as a multi-item measure of disease activity in all future clinical trials in paediatric CD.

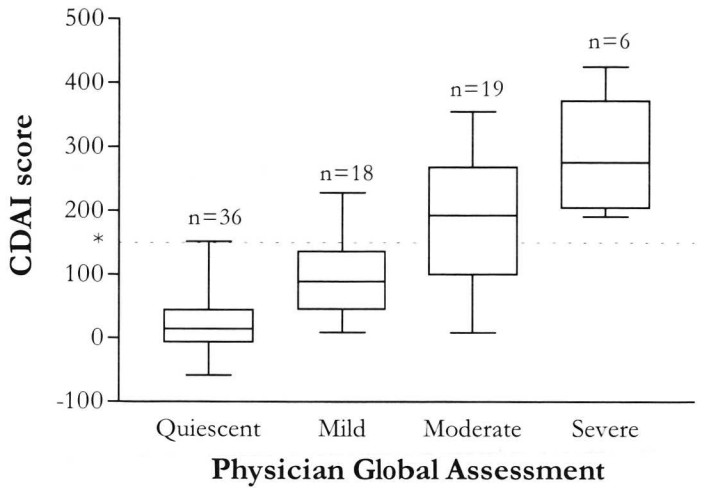

Figure 2.

Box-and-whisker plot of CDAI scores among patients categorized by physician global assessment of disease activity. The box shows the 25th percentile, median, and 75th percentile. The whiskers show the range of the data. The CDAI score could not be calculated (diary not available) for 1 patient (moderate).
* CDAI cut score for inactive disease (< 150).[2]

The benefits of the PCDAI with respect to feasibility are clear-cut. The PCDAI is easy to complete at the time of a patient's visit. The children and adolescents in our study showed difficulties prospectively completing the 7-day CDAI diary card before a clinic visit. In the context of a randomised controlled trial, parents are often hesitant to delay initiation of treatment so that the CDAI can be calculated before study entry. Obviation of such a record will facilitate patient recruitment into clinical research protocols.

The reliability of an instrument refers to its reproducibility.[12] Measurement variability is present when different results are obtained on repeated measurement of the same entity. An instrument cannot be valid unless it is reproducible. We did not reassess the reliability of the PCDAI because a previous assessment indicates that it is good. In the study by Hyams et al.,[5] 131 patients at 14 different hospitals were evaluated by a pair of paediatric gastroenterologists. Each physician evaluating a patient was blinded to the assessment of the other examining physician. There was excellent correlation between two physicians using the total PCDAI to assess the same patient under the same circumstance (Spearman rank correlation coefficient, 0.86), despite weaker correlation for individual items, notably abdominal examination (Kendall's t, 0.64).[5] A study among adult patients has documented that CDAI scores are not reproducible. [13] Considerable scatter of individual CDAI values was

observed by deDombal et al.[13] even among the most experienced clinicians and after intensive discussion regarding the use of the CDAI.

Comparisons of the PCDAI and the CDAI show why the former tool is more reliable. The PCDAI includes more objective data (laboratory parameters, height, and weight), which are less subject to uninformative variability. Subjective variables contribute only 20% to the maximal possible score of 100 on the PCDAI but roughly 39% to the CDAI. Furthermore, in the CDAI, individual observer ratings of items are multiplied by coefficients, thereby making minor discrepancies much larger for heavily weighted items.[13]

Validity addresses the issue of the degree of confidence that can be placed in inferences drawn from scores on scales.[14] A high PCDAI score should imply a high level of intestinal inflammatory activity and a low-score quiescent disease. Validity assessment begins with careful qualitative appraisal of an instrument to consider whether the included items truly contribute to what is being measured. The domains of the PCDAI chosen to constitute disease activity are abdominal pain, altered stool pattern, general well being, weight, linear growth, peri-anal disease, extra intestinal manifestations, abdominal examination, and laboratory parameters of inflammation. There are some inappropriate inclusions. Peri-anal disease often runs a course separate from the intestinal inflammation and requires its own treatment. A separate index of peri-anal disease activity has been proposed.[15] Secondly, although linear growth is an important parameter by which to judge activity of disease in children, height changes more slowly than other parameters included in the index. Inclusion in an index to be evaluative over a relatively short interval, as in most trials of drug efficacy, may be problematic.

There is no true gold standard of CD activity against which to validate either the PCDAI or CDAI. The present study confirms the observations of Hyams et al.[5] that the PCDAI is strongly correlated with physician global assessment. Although the CDAI also correlates well with physician global assessment, it more often incorrectly classifies disease activity. Patients with disease of mild and even moderate severity may score in the quiescent range if they fail to report symptoms in the heavily weighted diary component of the measure. The correlation of the PCDAI with laboratory parameters was superior to that of CDAI. Given that all laboratory measures of CD activity are imperfect, excellent correlations would not be expected.[16,17]

This study provides additional data indicating the significance of numerical values, information that is essential in the selection of inclusion and exclusion criteria and in defining clinical remission in efficacy trials. The data support the originally specified PCDAI value of > 30 for moderate and severe disease. The requirement of a PCDAI of ≤ 10 as an indicator of inactive disease appears to be too stringent. A value of < 15 could prove to be superior.

One performance characteristic of the PCDAI that has not been examined previously is its responsiveness. Responsiveness, "the ability to detect clinically important change," is extremely important for an evaluative instrument such as the PCDAI and is best studied in the

context of a randomised controlled trial.[18] The ability to detect a treatment effect is assessed because change over and above a control group is measured. Our study provides initial evidence, in a subgroup of patients assessed longitudinally, that the PCDAI does change even in a short period of time when the disease activity changes. This is reassuring because of the concerns about inclusion of linear growth in an index that is to be evaluative in drug trials of typically 4–6 weeks' duration. One can accept this item as an inappropriate inclusion if responsiveness of the measure is nevertheless good.

Although the PCDAI was validated previously as an evaluative instrument, paediatric investigators have been slow to adopt it in the assessment of disease activity. Our study indicates that, in comparison to the CDAI, the PCDAI is a more feasible multi-item measure that more validly reflects the severity of intestinal inflammation in paediatric patients. We have provided further information regarding significance of individual scores and evidence in support of the tool's responsiveness. Future trials in children and adolescents with CD should use the PCDAI as an outcome variable.

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