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REGULAR ARTICLE

The prospective association between behavioural problems and asthma outcome in young asthma patients

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ABSTRACT

Aim: The aim of this prospective study was to examine the association between behavioural problems and medical and psychological outcomes in clinically treated children and adolescents with asthma.

Methods: Patients (n = 134) were recruited from two high-altitude asthma clinics in Switzerland and one asthma clinic in the Netherlands. Outcome measures were Asthma Control Test (ACT), Paediatric Asthma Quality of Life Questionnaire (PAQLQ(S)), forced expiratory volume in 1 sec (FEV_1) and fractional concentration of exhaled nitric oxide (FeNO). Parents completed the Child Behaviour Checklist (CBCL) (predictor variable). Data were collected at the start and end of treatment. Multiple regression analysis was used while adjusting for demographic variables, clinic and length of stay.

Results: More severe internalizing behavioural problems were associated with less improvement of total quality of life ($t = -2.26$, $p = 0.03$) and the domains symptoms ($t = -2.04$, $p = 0.04$) and emotions ($t = -2.3$, $p = 0.02$) after clinical treatment. Behavioural problems were not associated with a change of lung function measurements (FEV_1 and FeNO) and asthma control (ACT) during treatment.

Conclusion: A focus of healthcare professionals on the treatment of internalizing behavioural problems may optimize the quality of life in clinically treated youth with asthma.

INTRODUCTION

Although many children and adolescents with asthma function well, selected children and adolescents with asthma may have behavioural problems, especially internalizing problems such as being withdrawn and depressed (1). These behavioural problems possibly affect the outcome of asthma treatment through multiple, complementary pathways. Behavioural problems and patients' beliefs about their illness may cause poor adherence, poor asthma management, poor functional health status (2,3) and delay in seeking medical help (4). Furthermore, psychosocial stressors may trigger the expression of asthma, for example, through neuroendocrine and immune mechanisms (5). Conversely, the burden of disease may lead to behavioural problems such as difficulty in separation and individuation from parents and associated anxiety (6).

Over the past decade, the emphasis in asthma management has shifted from treatment decided by level of asthma severity to therapy aimed at achieving full control of asthma (7). Full control comprises a combination of little or no asthma symptoms (day and night), little or no use of reliever medication, no restriction of activities, no exacerbations and normal lung function (8). Behavioural factors such as illness perceptions, the cognitive-emotional

Key notes

- In clinically treated children and adolescents with asthma, internalizing behavioural problems before treatment are associated with a lower increase in quality of life during treatment.
- Next to a biomedical focus, a focus of healthcare professionals on the treatment of internalizing behavioural problems may optimize quality of life in children and adolescents with asthma.

representation of asthma symptoms and management have been observed to influence asthma outcome (3). This suggests that complementary to medical care, targeting behavioural problems could possibly help patients with a psychological risk profile to better manage the disease.

Although in cross-sectional studies psychological variables have been shown to be associated with clinical asthma outcome, studies of the *prospective* association between behavioural problems and asthma outcome are scarce and show equivocal results. Family routines predicted asthma outcome (9), and parental stress and depression at baseline were associated with subsequent increases in children's inflammatory profiles over a 6-month period (10). It is not known whether behavioural problems in children and adolescents are prospectively associated with asthma outcome during clinical treatment.

The aim of our study was to examine the association between behavioural problems and the subsequent biomedical (lung function) and perceived (control of asthma and quality of life) outcome in a longitudinal design. We expected to find less improvement of asthma control, quality of life and lung function during treatment in children and adolescents with more severe behavioural problems at the start. Our prospective study was conducted in a heterogeneous sample of children and adolescents clinically treated at high altitude or sea level.

METHODS

Study population

Patients were children and adolescents with asthma who were admitted for clinical treatment in one of three clinics: two high-altitude asthma clinics with a hypo-allergenic environment in Switzerland, the *Netherlands Asthma Centre Davos* (Dutch asthma clinic, hosting Dutch patients) and the *High Altitude Clinic Davos* (German asthma clinic, hosting German patients), and one clinic at sea level in the Netherlands, the *Asthma Centre Heideheuvel* (hosting Dutch patients). From 2008 to 2010, all children aged 7–18 years with a confirmed diagnosis of asthma were invited to participate in the study.

Treatment

The participating clinics provide care for children with difficult-to-treat asthma with allergy for one or more inhaled allergens, bronchial hyper-responsiveness and eczema or other presentations of the atopic syndrome commonly being present (11). The reason for referral to one of the centres by the local or academic paediatrician or paediatric pulmonologist is often the coexistence of multiple asthma-related problems and the need for an extensive multidisciplinary approach.

The three clinics provide integrated multidisciplinary treatment programmes of 1–3 months. A standard diagnostic programme is performed with both somatic and psychosocial investigations. The children participate in a group psycho-educational asthma programme that aims to increase knowledge, technical skills (inhalation technique) and coping strategies. Besides, they have individual therapeutic contacts with a paediatric pulmonologist or paediatrician, pulmonary nurse, physical and sports therapist, pedagogical worker, psychologist and social worker. If possible, the parents participate in an educational programme.

Several factors are unique to the treatment in Davos, Switzerland. In contrast to children treated at sea level in Hilversum, the Netherlands, the children in Davos temporarily live in a hypo-allergenic environment due to a lower concentration of pollen and almost complete absence of house dust mite (12). The German high-altitude clinic has a more exclusive focus on medical pulmonary treatment. The patients in Switzerland live separated from their family and their own social network. They all remain there for the whole treatment period (including the weekends). In contrast, the children in Asthma Centre Heideheuvel are at home every weekend.

Procedure

The medical ethics committee of the Academic Medical Centre (AMC), Amsterdam, the Netherlands, approved the study. The children ≥ 12 years of age and the parents of all children provided written informed consent.

Two weeks before the start of treatment in one of the three clinics, patients with asthma and their parents received paper-and-pencil questionnaires at their homes. On arrival of the patients at the clinic, medical history was taken including atopic symptoms, exercise intolerance, medication, reliever therapy and adherence. Lung function testing (spirometry) and inflammometry (FeNO) were performed. History and physical examination were performed by one selected paediatrician per clinic. The diagnosis of asthma was approved or rejected on the basis of history, examination and confirmed bronchoconstriction with (partial) reversibility in history.

At discharge, the self-report questionnaires (self-administered) of patients and lung function and airway inflammation measurements were repeated.

Instruments

Predictor variable

Parental report: emotional and behavioural problems. The Child Behaviour Checklist (CBCL) is a standardized questionnaire for assessing emotional and behavioural problems of children by parents or caregivers (13). Parents of the children and adolescents filled out the Dutch 2001 version of the CBCL (6–18 years) or the 1998 German version of the CBCL (4–18 years) (14). The CBCL consists of 120 questions, range 0–2 per item. Results of the CBCL are expressed in a global score (120 questions, range 0–240) and in scores for internalizing (32 questions, range 0–64) and externalizing (35 questions, range 0–70) behavioural problems. We used the raw scores of the CBCL in our analyses. Higher scores indicate more behavioural problems.

Outcome variables

Children's self-report: quality of life. The Paediatric Asthma Quality of Life Questionnaire, PAQLQ(S), is a widely used disease-specific health-related quality of life self-report measure for children and adolescents aged 7–17 years (15). The Dutch PAQLQ(S) has adequate psychometric properties and excellent responsiveness, which supports longitudinal and cross-sectional construct validity (16). The PAQLQ(S) is responsive to change of asthma control and has strong measurement properties (17). The questionnaire assesses three domains: symptoms (10 items), activity limitations (5 items) and emotional function (8 items). The item range of 1–7 is reported per domain and for the whole instrument. Higher scores indicate better quality of life (15).

Children's self-report: asthma control. The childhood Asthma Control Test (ACT) (18) is a 7-item checklist, with a maximum score of 27 points. This questionnaire shows the control of asthma at the moment of measurement, reported by the child (four questions) and their caregivers. Only the raw scores of the four child questions (self-report) with a range from 0 to 12 were assessed at the start of treatment and at discharge.

Lung function. Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Hoechberg, Germany). A standardized protocol with at least three technically correct manoeuvres was performed. Short or long acting β_2-adrenergic agonists were stopped 12 h before PFT. The lung function parameter that was obtained and evaluated was forced expiratory volume in 1 sec (FEV_1).

Airway inflammation was measured with the Niox Flex (Aerocrine, Sweden) using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS and ERS guidelines (19).

Statistical analysis

Statistical analyses were done with SPSS 17.0. p-values < 0.05 (2-sided) were considered statistically significant.

The score distributions were checked for outliers and normality. Outliers ($z > 3.29$) were detected for the CBCL scales total (2 outliers), internalizing (1 outlier) and externalizing (4 outliers) problems at the start of treatment and the PAQLQ(S) scale 'emotions' (2 outliers) at discharge. These outlying variables were assigned a score that was one unit larger than the next most extreme score of the score distribution (20).

The characteristics of the three treatment groups were compared using univariate analysis of variance with pairwise Bonferroni comparisons in case of significant group differences. The gender distribution of groups was compared using a chi-square test.

Paired samples *t*-test and univariate analysis of variance were used to examine the pre-to-post treatment change in outcome variables. Because the outcome of asthma treatment at high altitude and sea level may differ (21,22), we adjusted analyses for clinics. Also patient characteristics that were correlated with the outcome were defined as a covariate.

Linear regression analysis was used to predict the treatment outcome as a function of behavioural problems (CBCL), while controlling for treatment clinic. Clinics were dummy-coded using codes for the Netherlands Asthma Centre Davos (1 = Yes, 0 = No) and for the High Altitude Clinic Davos (1 = Yes, 0 = No). Thus, patients of the Asthma Centre Heideheuvel obtained a value of zero on these variables. Control variables that were significantly related to at least a single outcome variable were entered in the analyses. In the first block of the regressions, the baseline score of the outcome variables was entered; as a consequence in the next blocks, the baseline-adjusted change score at the outcome variable was predicted. In the second block, the patient characteristics were entered. In the third block, the clinic was entered, and in the fourth block, the length of stay in the clinic. In the final block, the behavioural problems were entered. The prediction variables 'total behavioural', 'internalizing' and 'externalizing' problems were entered in separate regression analyses.

RESULTS

Patient characteristics

Fifty-one of 62 (82%) Dutch clinical patients of the Netherlands Asthma Centre Davos were included; four patients did not provide informed consent, the parents of six patients did not complete the Child Behaviour Checklist (CBCL) questionnaire and in one patient the diagnosis asthma was withdrawn. Of 63 German clinical patients of the High Altitude Clinic Davos, 48 were included (76%); three patients did not provide informed consent, 10 did not complete the CBCL and in 2 the diagnosis asthma was withdrawn. Thirty-five of 40 (88%) Dutch clinical patients of Asthma Centre Heideheuvel participated in our study; 2 did not provide informed consent, 2 did not respond and one did not complete the CBCL.

Table S1 shows the characteristics of 134 patients with a complete data set and a certified diagnosis of asthma at the start of treatment in one of the three asthma clinics. The mean age of the total group was 12.9 (SD 2.7, range 7–18) years, with 52% girls.

The children and adolescents in the three groups did not significantly differ with respect to percentage of girls ($\chi^2 = 0.53$, $p = 0.77$) and mean age ($F = 0.54$, $p = 0.59$). The mean length of stay was longer in the Dutch (Netherlands Asthma Centre Davos and Asthma Centre Heideheuvel) patients as compared to the German (High Altitude Clinic Davos) patients ($F = 33$, $p < 0.001$). Behavioural problems did not differ significantly at the start of treatment between the three groups (total score, $F = 0.63$, $p = 0.54$; internalizing problems, $F = 0.39$, $p = 0.69$; externalizing problems, $F = 0.24$, $p = 0.79$). FEV_1 measurements projected in the normal range, but showed significant differences between clinics ($F = 3.38$, $p = 0.04$). FeNO did not

differ ($F = 1.79$, $p = 0.17$). Control of asthma (ACT) differed ($F = 18.51$, $p < 0.001$) between clinics. Quality of life (PAQLQ(S)) did not significantly differ with respect to the total score ($F = 1.83$, $p = 0.16$) and the domain 'emotions' ($F = 1.11$, $p = 0.33$), but the domains 'symptoms' ($F = 3.14$, $p = 0.05$) and 'activity' ($F = 3.63$, $p = 0.03$) differed significantly.

Treatment effect

Table S2 shows the lung function measurements (FEV_1 and FeNO), control of asthma (ACT) and quality of life (PAQLQ(S)) scores at the start and end of treatment per clinic. Table S3 shows the standardized baseline-adjusted pre-to-post therapy change scores.

FEV_1 did not significantly change in any group. FeNO improved significantly in all groups (Table S2); the differences between clinics were not significant (Table S3).

Control of asthma improved significantly in the populations of the Netherlands Asthma Centre Davos and the Asthma Centre Heideheuvel (Table S2) and improved significantly more in the Netherlands Asthma Centre Davos than in the other clinics (Table S3). All domains of quality of life improved significantly in all groups (Table S2). The patients of the Netherlands Asthma Centre Davos improved significantly more than the patients of the High Altitude Clinic Davos on total quality of life (Table S3).

Prospective associations

Asthma control

Table S4 shows the results of linear regression analyses predicting asthma outcome (lung function and control of asthma) from age, clinic, length of stay and behavioural problems. In the first block, baseline scores were shown to be associated with post-treatment scores at a high significance. Having controlled for baseline scores, in the subsequent blocks, the baseline-adjusted change at the outcome variable was predicted. In block 2, a higher age was just not significantly associated with less improvement of lung function (decreased FEV_1, $t = -1.93$, $p = 0.06$ and increased FeNO, $t = 1.90$, $p = 0.06$). In block 3, being treated at the Netherlands Asthma Centre Davos was associated with more increase of control of asthma ($t = 3.54$, $p = 0.001$), and in block 4, a longer length of stay was associated with increased control of asthma ($t = 3.20$, $p = 0.002$). In block 5, more severe externalizing problems were not significantly associated with decreased FeNO ($t = -1.67$, $p = 0.098$).

Quality of life

Table S5 shows the longitudinal associations of age, clinics, length of stay and behavioural problems with quality of life.

In block 2, a younger age was significantly associated with more increase of total quality of life ($t = -2.00$, $p = 0.05$) and more improvement on the domains symptoms ($t = -2.29$, $p = 0.02$) and activity ($t = -2.04$, $p = 0.04$). In block 3, being treated at the Netherlands Asthma Centre Davos was associated with better scores on quality of life improvement: total quality of life (just not significant: $t = 1.93$, $p = 0.06$) and the domains symptoms ($t = 2.32$, $p = 0.02$) and activity ($t = 2.37$, $p = 0.02$). Being treated at the High Altitude Clinic Davos, Switzerland was associated with more improvement on the domain emotions ($t = -2.13$, $p = 0.04$). Duration of treatment (block 4) was not significantly associated with more improvement of quality of life. In block 5, more severe internalizing behavioural problems were associated with less improvement of total quality of life ($t = -2.26$, $p = 0.03$) and the domains symptoms ($t = -2.04$, $p = 0.04$) and emotions ($t = -2.33$, $p = 0.02$).

DISCUSSION

This prospective study examined the association between behavioural problems in children and adolescents with asthma at the start of clinical treatment and the outcome of asthma after treatment. The main analysis of our study showed that more severe internalizing behavioural problems were associated with less increase of quality of life after clinical treatment; asthma improvement was not associated with behavioural problems. Younger age was associated with improvement of quality of life. Longer length of stay was associated with increased control of asthma.

Outcomes were analysed in patients treated at high altitude and in patients treated at sea level. FeNO improved, control of asthma improved in two clinics and quality of life improved in all clinics. We did not find an improvement in FEV_1; measurements at the start of treatment were already in the normal range. While improvement in airway inflammation during a stay at high altitude might occur independent of pharmacological treatment or severity of the disease (21), in the current study airway inflammation (FeNO) improved in the whole sample, without a significant difference between the clinics.

On average, asthmatic children have a significantly poorer quality of life than children from the general population (15), especially children with problematic severe asthma (1,23). Asthma control test scores are also lower in problematic severe asthma compared with controlled asthma (23). In our study, control of asthma and the total quality of life improved most in the patients treated in the Netherlands Asthma Centre Davos. A previous study also suggested that quality of life improved more during clinical treatment in a hypo-allergenic environment than at sea level (22). Our present study replicates this finding for the Dutch, but not for the German high-altitude clinic. This may suggest that the improvement in quality of life is not due to treatment at high altitude per se. However, also the short length of stay may have played a role here. Furthermore, the more positive effects on asthma control and quality of life in the Dutch compared with the German high-altitude clinic could be due to the more exclusive focus on integrative medical and psychological treatment in the Dutch high-altitude clinic. The current study, however, was not designed to compare the clinics. Perhaps the combination of high-altitude treatment and treatment by a

multidisciplinary team is especially effective to improve quality of life.

Age was not significantly associated with improvement of lung function. However, a younger age was associated with an increase in total quality of life and an improvement in the domains symptoms and activity. Longer treatment duration was associated with a larger increase of asthma control. Although this observation might reflect that a longer stay is better to achieve asthma control, it is also possible that the medical specialist correctly appraised which patients could better stay longer because benefit in terms of asthma control was still possible. It is also possible that the child experiences increased asthma control as a justification for a longer stay in the clinic (cognitive dissonance theory).

Because treatment allocation was not random, we cannot conclude that this reflects that a treatment programme of relatively long duration is necessary to improve asthma control.

More severe internalizing behavioural problems predicted less increase in total quality of life after treatment, specifically a less positive change in the domains symptoms and emotions. This was the core question of our study. Behavioural problems might have an effect on asthma through multiple, complementary mechanisms, such as neuroendocrine stress responses affecting immune processes that influence asthma (2), poor asthma management such as poor adherence to asthma medication and poor functional health status such as having a sedentary life style (24). In our previous cross-sectional study, we observed that behavioural problems were associated with more severe asthma, suggesting that a focus on behavioural problems might be beneficial for asthma control (1). Our current study showed that behavioural problems did not obstruct the outcome of asthma. Thus, our results suggest that treatment of behavioural problems might be useful to improve quality of life, while no effects on the outcome of asthma are to be expected.

Our study has strengths and limitations. The children and adolescents of our study represent a population that was referred to specialized asthma clinics, which limits the generalizability of our results to a general asthma population. Moreover, with respect to comparison of clinics, our study was descriptive. The three specialized clinics differ regarding the educational programme, the location at high altitude or sea level and the duration of treatment. In regression analysis involving outcome prediction from behavioural problems, we adjusted for these differences between clinics. However, random allocation to clinics would have been needed to make a true comparison of treatment effects between clinics. Earlier research suggested that the inclusion of both Dutch and German patients will not have influenced the behavioural problem scores to a large extent (25,26). Strength of our choice to use parental ratings to assess behavioural problems is that parents are more objective observers than children (27). A major strength of our study is the prospective design and the adjustment for covariates in regression analysis.

Our study indicates that more severe internalizing behavioural problems are associated with less improvement of quality of life during clinical treatment. In children with chronic diseases including asthma, there is evidence of effectiveness for interventions incorporating cognitive-behavioural techniques on variables such as self-efficacy, self-management of disease, family functioning, psychosocial well-being, reduced isolation, social competence and days absent from school (28). Cognitive-behavioural interventions are the more indicated in the selected group of children and adolescents with behavioural problems.

In conclusion, the findings of the present study in a clinically treated population with asthma indicate that healthcare professionals should focus on the treatment of internalizing behavioural problems to optimize the quality of life of children and adolescents with asthma.

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CONFLICT OF INTEREST

No conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Characteristics of the 134 patients with asthma at the start of treatment.

Table S2 Mean scores (SD) and p-values at the start and end of treatment per clinic: Lung Function measurements FEV_1 and FeNO, Control of Asthma (ACT) and Quality of Life (PAQLQ(S)).

Table S3 Standardized baseline-adjusted pre-to-post therapy change scores per clinic: Mean (standard error) and p-values of Lung Function, Control of Asthma and Quality of Life scores.

Table S4 Results of regression analyses predicting asthma outcome (lung function and control of asthma) from baseline scores (block 1), person characteristics (block 2), clinic (block 3), length of stay (block 4) and behavioural problems (block 5).

Table S5 Results of regression analyses predicting quality of life from baseline scores (block 1), person characteristics (block 2), clinic (block 3), length of stay (block 4) and behavioural problems (block 5).