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Long term morbidity and health related quality of life after multi-system Langerhans cell histiocytosis

Vasanta Rao Nanduri[a,b,e,*], *Jon Pritchard*[c], *Gill Levitt*[a], *Adam W. Glaser*[d]

[a]*Department of Haematology/Oncology, Great Ormond Street Hospital for Children, London WC1N, UK*
[b]*Department of Endocrinology, Great Ormond Street Hospital for Children, London WC1N, UK*
[c]*Department of Oncology and Haematology, Royal Hospital for Sick Children, 17 Millerfield Place, Edinburgh EH9 1LW, UK*
[d]*Yorkshire Regional Centre for Paediatric Oncology and Haematology, St James University Hospital, Beckett Street, Leeds LS9 7TF, UK*
[e]*Department of Paediatrics, Watford General Hospital, Vicarage Road, Watford WD1 8HB, UK*

ARTICLE INFO

Article history:
Received 4 April 2006
Accepted 1 May 2006
Available online 7 September 2006

Keywords:
Histiocytosis
Langerhans cell histiocytosis
Sequelae
Late effects
Morbidity
Quality of life
Health status
Permanent consequences

ABSTRACT

Background: Langerhans' cell histiocytosis, a clonal multisystem disorder, can affect children or adults resulting in long term sequelae. However, the overall morbidity for survivors has not been formally determined.

Patients and Methods: We performed a cross-sectional study of 40 unselected long term survivors of childhood multisystem Langerhans cell histiocytosis, involving clinical examination, health–related quality of life assessment, brain imaging, neuropsychometry, endocrine assessment, respiratory function tests and audiometry. A specific 'morbidity score' was devised to measure outcome.

Results: Seventyfive percent of patients had detectable long term sequelae, hypothalamic-pituitary dysfunction (50%), cognitive dysfunction (20%) and cerebellar involvement (17.5%) being the most common. Half had moderate to severe morbidity, and the worst-affected patients were unable to lead an independent adult life. Health-related quality of life, which correlated well with the morbidity score ($p < 0.001$), was adversely affected in >50% of patients.

Conclusion: Organ damage from multisystem Langerhans cell histiocytosis causes long term morbidity extending into adult life. Carefully planned, multidisciplinary follow up is essential to ensure early recognition of problems with appropriate interventions to reduce the impact on patients' 'quality of life'.

1. Introduction

Langerhans' cell histiocytosis (LCH) is a granulomatous disorder characterised by clonal proliferation of pathological CD1a-positive Langerhans' cells accompanied by other inflammatory cells in various tissues during the active phase, which can last from a few months to several years.[1] Scarring can occur in various organs resulting in sequelae including hypothalamic-pituitary deficiency, deafness, proptosis, tooth loss, lung and liver fibrosis and neurological abnormalities.[2–4] Currently there is no system that is both suited to the assessment of overall morbidity and that provides a useful measure of health outcome for these patients.

Assessment of a patient's perception of the burden of their disease and its treatment on their life is important, and outcome measures are increasingly incorporated into clinical trials. However, it is still difficult to define 'quality of life' in children and young people and even harder to measure it

* *Corresponding author:* Tel.: +44 1923 217992; fax: +44 1923 217279.
E-mail address: vasanta.nanduri@whht.nhs.uk (V.R. Nanduri).
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doi:10.1016/j.ejca.2006.05.031

and assess its implications for any individual. Several methods have been suggested for this subjective measure, but none can yet be considered as the 'gold standard'. 'Health-related quality of life' or 'health status' has the advantage of exploring the impact of both disease and treatment but excludes factors such as spirituality, environment and financial issues.

The main aim of this aspect of the study was to assess the subjects' quality of life, to develop an instrument (Langerhans cell histiocytosis morbidity score) to measure the burden of disease in survivors and to determine whether a professional's assessment of 'morbidity' correlated with patients' and parents' views of their health-related quality of life.

2. Patients and methods

We conducted a cross-sectional multi-disciplinary follow up study of survivors of biopsy-proven multisystem LCH, all at least 5 years from the end of treatment. During the period 1966–1998, 275 patients with LCH were seen at the hospital. Of the 147 with multisystem involvement, 36 died, leaving 111 survivors of whom 59 were less than 5 years from the end of treatment for LCH. Therefore 52 patients (18.9% of entire cohort) fitted the selection criteria for the study as listed above. Twelve patients who fitted the selection criteria were excluded from the study for the following reasons: two patients had emigrated, three failed to attend their appointments and the rest could not be traced. There was no statistical difference with regard to systems involved, treatment received and duration of illness between these patients and those included in the study. The remaining 40 patients (21 boys and 19 girls) entered the study. Age at diagnosis ranged from 6 weeks to 15.5 years (median 17.5 months) and age at assessment from 7 to 31.1 years (median 16.4 yrs). Treatment during the 'active' phase of Langerhans cell histiocytosis had included one or more of the following: biopsy and/ or curettage of lesions in 19 patients, oral corticosteroids in 21 with cumulative doses of 38 mg/kg to 1000 mg/kg (median dose 150 mg/kg) over a duration of 2 months to several years, chemotherapy (etoposide, vinblastine, vincristine, cyclophosphamide and methotrexate) in 13, azathioprine in six, and radiotherapy to the region of the head in four. Two patients had received 1200 cGy to the pituitary region at ages 8 and 10 years, one patient had received 1200 cGy to the orbit at age 6 years and one patient had received 1200 cGy to the pituitary and an additional 300cGy boost to an occipital skull lesion at 6 years.

The period of follow up after completion of therapy was 5 to 23 years (median 11.2 yrs).

Approval for the study was obtained from our Institutional Research Ethics Committee. Informed written consent was provided by each patient and/or their parents.

Patients underwent clinical examination including anthropometry and assessment of puberty, endocrine function, neurological assessment including grading of ataxia,[5] audiology, respiratory function tests, magnetic resonance imaging of the brain, computed tomography of the skull and measurement of cognitive function.

Some of the results involving specific systems – endocrine deficiencies, skin, skull base abnormalities and cognitive function- have already been published.[6–9] In this paper we focus on the assessment of overall 'morbidity' and health–related quality of life.

2.1. *Langerhans cell histiocytosis morbidity score*

The various systemic sequelae considered relevant in long term follow up of patients were categorised into six sections, as follows:

a) hypothalamic-pituitary deficiencies
b) neurological motor abnormalities
c) learning deficit and psychological disturbance
d) hearing loss
e) pulmonary dysfunction
f) cosmetic problems

Each category was then assigned four grades of severity (0–3), depending on the degree of morbidity and the need for treatment (Table 1). Sequelae in each patient were graded according to this classification and summated to form a total morbidity score. This cumulative score was graded as – 'normal' (0), 'mild' (1–4), 'moderate' (5–10) or 'severe' (11–18).

2.2. *Assessment of health-related quality of life (health status)*

The Health Utilities Index[11] was self-completed to assess health-related quality of life. Seven of the 40 patients were under 12 years at the time of the study and one patient now resides abroad and was unavailable. Results from the other 32 patients were analysed.

2.2.1. *Questionnaires*

A cross-sectional postal survey was performed. Components included a) the 15-item self-administered Health Utility Index questionnaire[11] and b) questionnaires on educational attainment in patients under 16 years, and on employment in those over 16 years.[12] Information from questionnaires was converted by an established algorithm to provide 'attribute levels' of the Health Utility Index mark 2 system.[10] The seven 'attributes' in this system are sensation, mobility, emotion, cognition, self-care, pain and fertility with three to five levels of function per attribute. The first six attributes were studied. Single-attribute utility scores and a global health status utility score were then calculated from the multi-attribute Health Utility Index system.[10] The utility scale for a single attribute ranges from 1.00 (normal) to 0.00 (most highly impaired) and the global health status utility scale ranges from 1.00 (perfect health) to 0.00 (death).

2.3. *Statistical methods*

Statistical Package and Service Solutions (SPSS) software was used for analysis. The 't' test was used to assess parametric data, while non-parametric data were analysed using the Mann–Whitney U test. The Pearson correlation coefficient was used to assess the relationship between the morbidity score and the health utility scale.

Table 1 – Langerhans cell histiocytosis morbidity score (this table gives details of scoring for the morbidity score and the grading of abnormality in each system)

Score	System
	Endocrine
3	Panhypopituitarism and/or hypothalamic syndrome not correctable with hormone replacement
2	Partial anterior pituitary deficiency / diabetes insipidus on replacement therapy
1	Partial diabetes insipidus, no replacement therapy
0	No pituitary deficiency
	Neurological (ataxia, motor deficit)
3	Severe ataxia (scale >40) or other motor disability
2	Moderate ataxia (scale 20–40)
1	Mild ataxia (scale <20)
0	No ataxia
	Education/ employment/ psychological
3	Severe learning difficulty (IQ < 70) and/or severe behavioural/psychological problems impairing function and not correctable by treatment
2	Moderate learning difficulty (IQ 71–79) and/or behavioural/psychological problems correctable by treatment
1	Mild learning difficulty (IQ 80–89) and/or mild behavioural/psychological problems not requiring treatment
0	Normal IQ, no behavioural problems
	Hearing deficit
3	Severe bilateral hearing loss, not correctable with aids
2	Moderate bilateral hearing loss, partially correctable by aids
1	Mild bilateral or moderate/ severe unilateral loss correctable with aids
0	No hearing loss or mild unilateral hearing loss, no aids required
	Pulmonary involvement
3	Severe exertional dyspnoea/ requiring lung transplant
2	Moderate exertional dyspnoea, restricting activity
1	Mild exertional dyspnoea, not restricting activity
0	No exertional dyspnoea
	Physical features/ facial/ dental/ scarring etc.
3	Gross facial or orthodontic abnormality and/or scarring requiring repeated or major surgery
2	Moderate facial or orthodontic abnormality and/or scarring correctable with surgery
1	Mild facial or orthodontic abnormality and/or scarring not requiring any surgery
0	No abnormality

3. Results

3.1. *Endocrine abnormalities and growth*

Hypothalamic-pituitary dysfunction was seen in 20 (50%) of the 40 patients, 19 of whom had diabetes insipidus[6] which developed within the first 5 years of diagnosis of LCH. In two of them polyuria and polydipsia preceded the diagnosis of LCH, but DI was confirmed on a water deprivation test only after LCH was diagnosed. DI preceded other hormone deficiencies in the majority of patients, the exception being those who had panhypopituitarism. Treatment interventions did not improve symptoms in any patients with established DI. Growth hormone insufficiency was present in 13 patients (32%), six of whom also had other anterior pituitary hormone deficiencies. Signs suggestive of hypothalamic damage including temperature instability, abnormal eating patterns and weight gain, irrational behaviour and 'rage attacks' were seen in five patients.

3.2. *Central nervous system abnormalities, behavioural and learning problems*

Ten (25%) patients had evidence of late neurological involvement, including ataxia and in-coordination, psychological problems and learning difficulty.[9] The time from diagnosis of histiocytosis to the first symptom of neurological damage ranged from 8 to 240 months (mean 112 months). There was no statistical correlation between neurological consequences and duration and types of treatment received, such as steroids or radiotherapy to the head. There was no statistically significant correlation between DI and CNS involvement.

Seven patients had cerebellar involvement with ataxia and in-coordination and bilateral signal changes on MRI in the dentate nucleus and cerebellar hemispheres. Eleven of 40 patients (27.5%) had behavioural and/or psychological problems and most required psychotherapy and/ or medication. Disorders included varying combinations of depression, anti-social behaviour, difficulties with inter-personal relationships, violent thought-processes, a fascination with 'fire-setting', and sexual fantasies. These features resulted in impaired capacity of some patients to form normal relationships and/or live independently.

3.2.1. *Cognitive outcome*

Patients with clinical neurological abnormality or MRI changes had significantly lower ($p < 0.001$) mean full scale, performance and verbal intelligence quotients and memory quotients.[9]

3.3. Bony abnormalities

Twenty-four (67%) of the 36 patients in whom bone lesions were identified during the 'active' phase of the illness had residual bony abnormalities at follow up. These patients had not received large doses of radiotherapy to the skeleton or excision of lesions, and the late effects appear to be disease-related rather than secondary to treatment. Abnormalities of the skull and/ or face included asymmetry ($n = 17$), residual bony defects ($n = 7$) (Fig. 1) and proptosis ($n = 7$). Four have marked distortion of the facial skeleton, for which reconstructive surgery is planned. Acquired basilar invagination was an unexpected finding in seven (17.5%) patients and might have long term implications.[8] Fifteen patients (37.5%) had loss of permanent dentition ranging from one to eight teeth. Ten patients (17.5%) required orthodontic correction, while two needed major reconstructive surgery.

None of the patients had evident limb abnormalities at follow up. In three of the six patients with vertebral involvement, vertebral height was almost completely restored, but the three others had residual vertebra plana.

3.4. Audiology and tympanometry

Of 28 patients with documented ear involvement during the 'active' phase of disease, 15 had residual permanent hearing loss. Six had unilateral hearing loss (four mild, two moderate hearing loss), and both ears were affected in nine cases, of whom four had severe deafness not correctable by hearing aids.

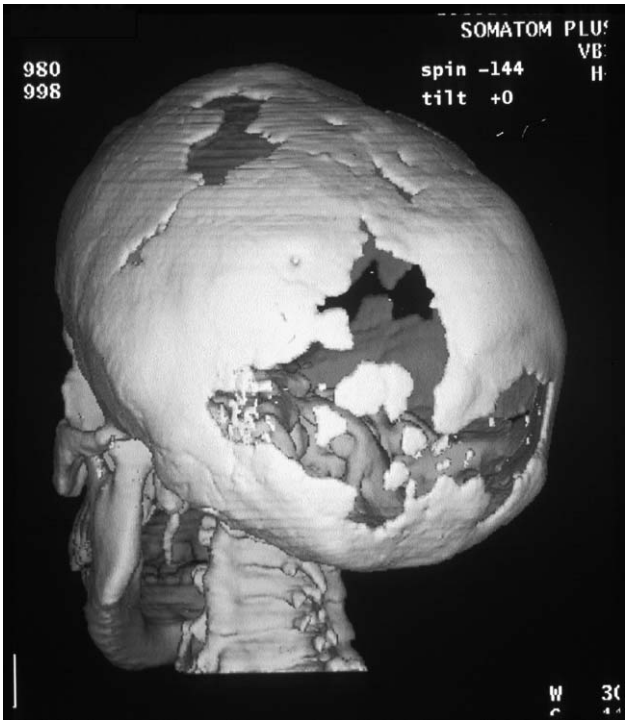

Fig. 1 – 3-Dimensional CT scan of the postero-lateral aspect of the skull showing multiple permanent skull defects 13 years after completion of treatment.

3.5. Skin sequelae

Of the 33/40 (82%) patients with skin involvement during the 'active' phase, scarring was noted at follow up in 15 patients. Eight patients had scars at sites of previous skin rash, while the other seven had scars from surgical procedures including biopsy, curettage, insertion of chest drains or orthopaedic and thoracic surgery. Four patients require surgical correction for scarring; One patient had chronic discharging sinuses overlying involved lymphnodes requiring excision, one had lipid-filled scars of juvenile xanthogranuloma, most obvious in the creases of the neck, one had several scars on the scalp with hair loss and underlying skull deficits and deep scars in the axillae and groin, and one had cosmetic surgery to remove a deep scar resulting from a discharging bony lesion. Apart from the scars from specific surgical procedures the rest of the scarring was disease-related rather than treatment related.

3.6. Pulmonary

Of 15 patients (37.5% of the cohort) with lung involvement during the 'active' phase, eight had abnormal lung function at follow up assessment, and five of them had breathlessness on exertion. Two patients had considerable restriction of functional ability and have been considered for lung transplantation. Each developed evidence of lung damage as young adults after they started to smoke. Chest X-rays and high resolution CT scans showed bilateral streaky interstitial shadowing, widespread fibrotic shadowing and multicystic change in the worst-affected patients. The relatively small numbers make it difficult to prove statistically, but there seems to be a tendency for more severe lung disease to be present in the patients who developed disease at an older age.

3.7. Morbidity score

Results are shown in Table 2. Physical and cosmetic problems were common and endocrine abnormalities, neurological damage and learning deficit each affected nearly half the patients. Deafness and pulmonary damage occurred less often. Overall, 10 patients (25%) had no sequelae (score 0); 11 (27.5%) had mild morbidity (scores 1–4), nine (22.5%) had moderate morbidity (scores 5–10), while 10 (25%) had severe disabilities affecting their capacity to live independently (scores > 11). The single most important indicator for outcome was the presence of neurological involvement. These patients fared significantly worse ($p < 0.005$) than those without brain involvement. Ataxia, intellectual deficit and psychological problems impaired their capacity to learn, to care for themselves and to integrate normally into society. Severe lung damage was a second cause of significant morbidity ($p < 0.005$). Individuals with the most severe morbidity had been treated for significantly longer (mean 6.05 years, range 0.49–20 years) than those with no, mild or moderate morbidity ($p < 0.05$). Interestingly, involvement of vital organs such as bone marrow, liver or spleen in the 'active' phase of the disease did not appear to be associated with long term morbidity. With the small numbers it was not possible to identify specific predictors of worse outcome apart from duration of treatment.

Table 2 – Results of Langerhans cell histiocytosis morbidity score (this table gives the results of the morbidity score in the study cohort)

Score	Abnormality	No. of patients	(%) of total cohort $n = 40$
	Endocrine		
3	Panhypopituitarism and/or hypothalamic syndrome	4	10
2	Partial anterior pituitary deficiency / diabetes insipidus	16	40
1	Partial diabetes, no anterior pituitary replacement	0	0
0	No pituitary deficiency	20	50
	Neurological (ataxia, motor deficit)		
3	Severe ataxia (scale > 40) or other motor disability	6	15
2	Moderate ataxia (scale 20–40)	3	7.5
1	Mild ataxia (scale < 20)	4	10
0	No ataxia	27	67.5
	Education/ employment/ psychological		
3	Severe learning difficulty/behavioural problems	7	17.5
2	Moderate problems	5	12.5
1	Mild problems	5	12.5
0	No problems	23	57.5
	Hearing deficit	3	7.5
3	Severe bilateral hearing loss	4	10
2	Moderate bilateral hearing loss	5	12.5
1	Mild bilateral or moderate/ severe unilateral loss	28	70
0	No hearing loss or mild unilateral hearing loss		
	Pulmonary involvement		
3	Severe exertional dyspnoea, on lung transplant list	2	5
2	Moderate exertional dyspnoea	2	5
1	Mild exertional dyspnoea	4	10
0	No exertional dyspnoea	32	80
	Physical features/ facial/ dental/ scarring etc.		
3	Gross abnormality requiring repeated or major surgery	5	12.5
2	Moderate abnormality correctable with surgery	7	17.5
1	Mild abnormality not requiring any procedures	10	25
0	No abnormality	18	45

3.8. *Health-related quality of life (health status)*

A total of 28 patients (87.5% of 32) returned completed questionnaires, 20 spontaneously and eight after a telephone prompt. There were no obvious demographic or treatment differences between the 'responders' and 'non-responders'. In eight patients, no attributes were adversely affected (i.e. scores of 1). In four patients, one attribute was affected (three scored 0.95 each for sensation, one scored 0.93 for emotion); seven patients reported that two of the following attributes (sensation, cognition, emotion, self care and pain) were affected, with scores ranging from 0.53 to 0.97; two patients that three attributes were affected, four that four attributes were affected, two patients that five attributes were affected, while the patient with the worst perceived 'quality of life'reported all six attributes as affected (scores 0.73–0.97). 'Emotion' was most commonly affected, but patients did not regard 'self-care' as a particular problem.

Overall health status utility score ranged from 0.48 to 1 (median 0.86, mean 0.88). The score was significantly lower ($p < 0.05$) in patients with brain involvement – (mean 0.73, SD 0.16) – than in those with no detectable brain involvement – (mean 0.91, SD 0.11) due to significantly lower ($p < 0.05$) attribute scores for sensation, cognition and emotion. There was a close correlation between intelligence quotient and global health status. Pulmonary involvement was also significantly associated with a low utility score, the two most severely affected patients scoring only 0.63 and 0.71, respectively. No other factor, such as duration of illness, treatment received or involvement of vital organs in the 'active' phase, correlated with health status.

There was an inverse correlation ($r = -0.73$, $p < 0.001$) between the morbidity score and utility scale (Fig. 2), indicating that the professional's assessment of morbidity correlated with the patients' impression of their own 'quality of life'.

3.9. *Education/ employment/ independent living*

All 20 patients under the age of 16 years are currently in full time education. However, two of them go to a special school for children with learning difficulties and one other child, though attending a mainstream school, receives extra academic help. Seven of the 20 patients aged over 16 years are still in full time education, but five have formally-acknowledged learning difficulties and attend courses in which they are taught skills required for independent living. Six patients are in full time employment and four in part time employment as they continue with their studies. Three patients are currently unemployed, one because of psychological dysfunc-

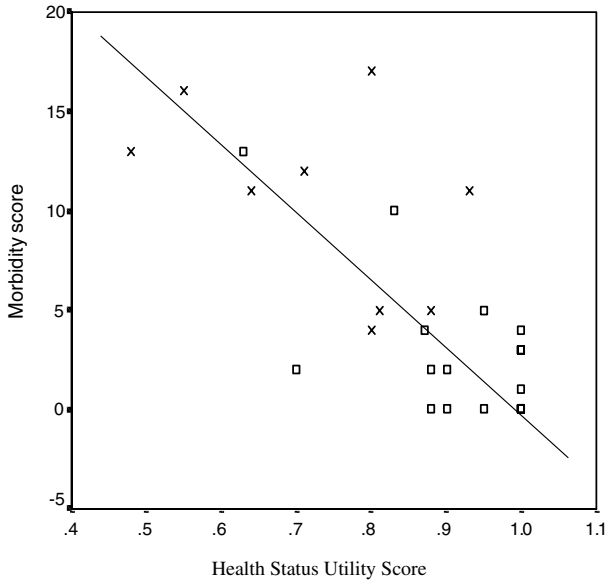

Fig. 2 – Correlation between Langerhans cell histiocytosis morbidity score and health status utility score. There was a close inverse correlation between the 'Langerhans cell histiocytosis morbidity scale' and health status utility score. ($r = -0.73$, $p < 0.001$). Patients with CNS involvement are identified by the x symbols, and those without CNS involvement by the □ symbols.

tion and two others because of both physical and emotional disability.

Six of the 20 patients (30%) aged >16 years receive state-provided financial benefits, the norm being 11–15% of the population. Sixteen of 20 (80%) patients aged >16 years still live with their parents. Of the four who live independently, one required warden-supervised accommodation because of his dependence on others until his death. Six of the 20 patients aged >16 years are in stable relationships with a partner.

4. Discussion

We have shown that survivors of childhood multisystem Langerhans cell histiocytosis have definite long term morbidity, with only 25% of patients being entirely well and nearly one half having permanent disease sequelae affecting the brain, hypothalamic-pituitary axis, lungs and/or bones. To develop a specific score of use to health professionals assessing these patients, we focussed on two different outcome measures in this study. The 'Langerhans cell histiocytosis morbidity score' represents a clinician's semi-quantitative view of functional outcome, whilst the Health Utilities Index measures the impact of the disease from the patient's perspective. 'Quality of life', which assesses the patient's perspective of burden of disease, is now recognised as an important outcome measure. We found that Langerhans cell histiocytosis has a significant impact on the patient's health-related quality of life. Domains most affected were emotion and cognition. Patients did not, however, feel that self-care was a problem, a surprising finding as several of the young adults were in special colleges where they were taught basic skills to help them to lead an independent life. Perhaps 'insight' is affected as a result of Langerhans cell histiocytosis damage to the brain.

It was encouraging to find that there is a close correlation between the two scales.

Using either measure – morbidity score or Health Utilities Index – brain involvement appears to be the single most important factor in determining outcome, with severe lung disease also causing significant morbidity. It is more difficult to assess the impact of facial dysmorphism and other morbidities on the 'quality of life' of these patients.

Further work on the measurement of long term morbidity and 'quality of life' in survivors is now needed. The international co-operative studies of treatment (The Histiocyte Society trials) will now incorporate measures of quality of life such as those used in this study to assist clinical follow up. Our 'morbidity score' is currently being used to assess outcome in centres in other countries and will help validate this system. Some modifications will likely be required to convert it into a truly international scoring system – a 'common language'. This form of assessment could be incorporated into clinical trials to provide a comprehensive picture of overall outcome for survivors of Langerhans cell histiocytosis, whom we have shown in this study to be at significant risk of late morbidity. Guidelines for managing the various types of handicap could then be developed and studied to improve final outcome. Our findings may also be relevant to assessing the functional outcome of children and adults with other chronic debilitating illnesses.

Conflict of interest statement

None declared.

Acknowledgements

We thank Prof. Ronald Barr, McMaster University, Canada for permission to use the Health Utilities Index, and Dr Richard Stanhope for his advice and encouragement throughout the project. Grant support for V.R. Nanduri: Ferring Pharmaceuticals and Jack's Pack.

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