Research Article

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Development and validation of a polycystic liver disease complaint-specific assessment (POLCA)

Frederik Temmerman[1,*], Fabienne Dobbels[2], Thien Anh Ho[3], Yves Pirson[3], Ragna Vanslembrouck[4], Walter Coudyzer[4], Bert Bammens[5], Jos van Pelt[1], Jacques Pirenne[6], Frederik Nevens[1]

[1]*Division and Laboratory of Hepatology, University Hospitals, KU Leuven, Belgium;* [2]*Division of Public Health and Primary Care, University Hospitals, KU Leuven, Belgium;* [3]*Division of Nephrology, Université Catholique de Louvain, Brussels, Belgium;* [4]*Division of Radiology, University Hospitals, KU Leuven, Belgium;* [5]*Division of Nephrology, University Hospitals, KU Leuven, Belgium;* [6]*Division of Abdominal Transplant Surgery, University Hospitals, KU Leuven, Belgium*

Background & Aims: Polycystic liver disease (PCLD) may lead to extensive hepatomegaly and invalidating complaints. Therapeutic decisions, including somatostatin-analogues (SAs) and (non)-transplant surgery are besides the existence of hepatomegaly, also guided by the severity of complaints. We developed and validated a self-report instrument to capture the presence and severity of disease specific complaints for PCLD.

Methods: The study population consisted of 129 patients. Items for the PCLD-complaint-specific assessment (POLCA) were developed based on the chart review of symptomatic PCLD patients (n = 68) and literature, and discussed during expert-consensus-meetings. 61 patients who needed therapy were asked to complete the POLCA and the short form health survey version 2 (SF36V2) at baseline and after 6 months of SA-treatment. CT-scans were used to calculate liver volumes (LV). Factor analysis was conducted to identify subscales and remove suboptimal items. Reliability was assessed by Cronbach's alpha. Convergent, criterion validity and responsiveness were tested using prespecified hypotheses.

Results: In the validation group (n = 61), 47 received lanreotide (LAN) and 14 were offered LAN as bridge to liver transplantation (LTx). Factor analysis identified four subscales, which correlated with the physical component summary (PCS). Baseline POLCA scores were significantly higher in LTx-listed patients. In contrast to SF36V2, POLCA-paired observations in 47 patients demonstrated that 2 subscales were lowered significantly and 2 borderline. LV reduction of $\geqslant$120 ml resulted in a numerical, more pronounced relative decrease of all scores.

Conclusions: In contrast to SF36V2, the POLCA shows good validity and responsiveness to measure complaint severity in PCLD.

Keywords: Hepatomegaly; Somatostatin-analogues; Liver transplantation; Health-related quality of life.

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* Corresponding author. Address: Division and Laboratory of Hepatology, University Hospitals, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Tel.: +32 16344299; fax: +32 16344387.

E-mail address: frederik.temmerman@uzleuven.be (F. Temmerman).

Abbreviations: PCLD, polycystic liver disease; SA, somatostatin analogue; LTx, liver transplantation; POLCA, PCLD complaint-specific assessment; SF36, 36-item short form health survey; CT, computed tomography; LV, liver volume; LAN, lanreotide; mTOR, mammalian target of rapamycin; ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; FDA, food and drug administration; PCS, physical component summary; MCS, mental component summary; GERD, gastro-oesophageal reflux disease; HRQL, health-related quality of life; IQR, interquartile range.

Introduction

Polycystic liver disease (PCLD) is a chronic inherited disorder in which numerous fluid-filled hepatic cysts are scattered throughout the liver. PCLD is the most frequent extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD). The second cause of PCLD is autosomal dominant polycystic liver disease (ADPLD), in which patients do not suffer from renal failure and only present with liver cysts. The natural history of PCLD, regardless of the genetic mutation, is similar [1–3]. Most of the patients with PCLD stay asymptomatic, but 2–5% of patients will develop symptomatic hepatomegaly as a result of the continuous increase in volume and number of liver cysts. The most frequently reported symptoms in the literature include abdominal distension, early satiety, abdominal pain, and finally severe malnutrition, which can be lethal. Some of these patients develop portal hypertension, ascites or Budd-Chiari like syndrome, but these complications are rather uncommon [2].

To reduce liver volume and improve complaints, several surgical techniques have long been the mainstream, including aspiration-sclerotherapy, laparoscopic or laparotomic fenestration and partial liver resection [4]. In patients with massive hepatomegaly and extreme invalidating symptoms, the only curative therapeutic option is liver transplantation (LTx) [5,6]. Pharmacological treatment of PCLD only became available five years ago. We and others showed that somatostatin-analogues (SAs), i.e., lanreotide and octreotide, decrease liver volume [7–10]. In addition, we recently demonstrated that a reduction of $\geqslant$120 ml in liver volume after 6 months has a high positive predictive value of improving complaints, a reduction, which lies above the 95% upper limit of the confidence intervals of the differences in LV

assessed by two software methods measuring the same LV [11]. Also mTOR inhibitors might reduce liver volume, although the data are less robust and a combination of octreotide and everolimus did not increase the LV-reducing effect of octreotide alone [3,12].

For the majority of patients, the hepatomegaly induced complaints represent the most important (referral) reason for medical or surgical treatment. Until now, this evaluation is almost exclusively made by physicians in a non-standardized way. Currently, there is no disease-specific questionnaire that (i) assesses presence, severity and impact of complaints in a standardized, valid way; (ii) can be used to assess the effect of pharmacological therapy; (iii) and finally is suitable to guide treatment decisions.

We aimed to develop and validate a questionnaire, the PCLD complaint-specific assessment (POLCA), intended to assess the specific complaints from the perspective of PCLD patients associated with hepatomegaly.

Patients and methods

In line with the FDA guidelines on the development of patient reported outcome measures, we first established a conceptual framework, in which we described the item generation process and psychometric properties (Supplementary Fig. 1) [13,14]. In line with the conceptual framework on symptom experience of Leventhal and colleagues, the questionnaire should be able to capture both the presence as well as the severity of complaints [15,16].

Study design

Item selection and content validity

We constructed an exhaustive list of items likely to represent complaints of hepatomegaly that could be perceived by patients with symptomatic PCLD, using two sources: (i) analysis of medical charts of 68 patients (creation group) referred for treatment between 1995–2007; and (ii) extensive literature search in PubMed, extracting complaints of PCLD reported in studies published between January 1997 and August 2010. Using search terms referring to the disease, its treatment forms and aspects of health-related quality of life, 15 articles were identified for data extraction [4,5,7,8,17–27].

In total, 27 candidate items were identified that were subsequently reviewed for relevance by an independent expert panel (three hepatologists, two nephrologists, and one abdominal transplant surgeon) and agreed upon during consensus meetings.

Next, based on evidence for optimal scaling of self-report instruments, a questionnaire was created with labelled Likert-type responses ranging from 0 to 5 for presence (0 = symptom not occurring; 5 = symptom present all the time), as well as for severity (0 = not; 5 = extreme severe) [28]. All items in this questionnaire were then critically evaluated by the same six experts for clarity (ease of understanding). This resulted in 16 items being part of the PCLD complaint-specific assessment (POLCA), of which 9 items referred to occurrence, and 7 items referring to perceived severity of complaints. Since PCLD is a rare disease, pretesting of the questionnaire in symptomatic PCLD patients was not performed in order not to lose patients for the instrument's validation. The POLCA is available in Supplementary Fig. 2 and as an online calculator (http://www.uzleuven.be/en/polca) alongside the LV-index calculator.

Validation group

The POLCA was administered only to symptomatic PCLD patients (n = 61) presenting at two different academic centres (University Hospitals, KU Leuven, Leuven and Université Catholique de Louvain, Brussels) for treatment initiation of which 54 participated in the open-label study to evaluate the safety and efficacy of LAN 90 mg, including a dose escalation to LAN 120 mg in case of non-responders (ClinicalTrials.gov identifier NCT01315795). A multidisciplinary board consisting of hepatologists, nephrologists, abdominal transplant surgeons, psychologist and social workers discussed each case. Treatment options in this study considered were: (i) LAN 90 or 120 mg every 4 weeks only; or (ii) LAN as a bridge to LTx. The latter group consisted of patients with a high subjective complaint burden due to hepatomegaly and who were considered not to be good candidates for other surgical interventions (e.g., Gigot type III or Mayo modification D) [29,30]. Patients considered as candidates for combined liver-kidney transplantation (cLTKTx; n = 5) were excluded to enhance the objectivity of hepatomegaly-related complaints.

The POLCA was administered to all patients prior to the choice of treatment and after 6 months. All data were collected and retrospectively analysed by a physician who was blinded for the multidisciplinary treatment decision at baseline and the patient's medical characteristics.

Informed consent was obtained from each patient. The use of the POLCA conforms with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the *a priori* approval by the institution's human research ethics committee.

Reliability and construct validity

Factor analysis was performed to determine whether the items measure a uni- or multidimensional concept. Next, reliability (internal consistency) of the subscales and the total scale were determined by Cronbach's alpha. To test for convergent validity, patients were administered the short form health survey version 2 (SF36V2) at baseline alongside the POLCA. The SF36V2 is a wildly used, norm-based validated survey that measures health status on 8 health domains (physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, emotional role functioning, social role functioning, and mental health). A physical component summary (PCS) and mental component summary (MCS) can be calculated [31,32]. We hypothesized that the POLCA subscales would correlate moderately with the more physically oriented health status domains, with correlation coefficients above 0.3 indicating good convergent validity. In view of known-groups validity, we hypothesized that patients on the waiting list for LTx will have higher POLCA subscale scores than patients not (yet) considered for transplantation.

Criterion validity

In order to determine the POLCA's concurrent validity, we hypothesized that patients with more complaints also had a larger liver. Therefore, at time of POLCA completion, a CT-scan without contrast enhancement was performed to calculate liver and kidney volumes. The CT-scans were performed on different multi-detector CT-scanners: Siemens Somatom Sensation 64 and Siemens Somatom Definition Flash (Siemens Medical Solutions AG, Erlangen, Germany), University Hospitals, KU Leuven; and Spiral/Helical CT Brilliance 64 (Philips), Université Catholique de Louvain, Brussels. Volumes were calculated by using Volume® (Siemens; Erlangen, Germany) by two radiologists who were blinded for the questionnaire data and treatment decision [11].

The LV was also 'normalized' to an enlargement index (LV-index), which gives an idea how many times the liver is enlarged for the individual patient; LV-index = liver volume (ml) (CT-scan)/[(706.2 × body surface area) + 2.4] [33]. We anticipated a moderate to strong correlation (r >0.50) as proof of concurrent validity.

Responsiveness

We hypothesized that changes in subscales of the questionnaire between baseline and 6 months were detectable and significant as a result of the pharmacological treatment. In addition, based on our previous observations, we also hypothesized that a reduction of $\geqslant$120 ml in LV after 6 months of SA-treatment results in a more pronounced effect on the perceived complaints [12].

Statistical analysis

Analysis of internal consistency was evaluated with Cronbach's alpha, with a value of >0.7 and <0.9 indicating excellent reliability. To analyse whether there were at least some correlations amongst the 16 POLCA items so that coherent factors are allowed to be identified, factorability was assessed by measures of sampling adequacy (Kayser-Mayer-Olkin >0.5). Factor analysis on eigenvalues was performed to identify subscales and remove suboptimal items, in which an eigenvalue <1 does not have enough total variance explained to represent a unique factor. To facilitate the interpretation of extracted correlated factors, promax rotation was used. Differences in characteristics between groups were analysed by an independent *t* test (two tailed) or Mann-Whitney U test, where appropriate. In order to evaluate responsiveness of the POLCA over time, a paired sample *t* test was used. To describe correlations, non-parametric testing by Spearman was performed. To compare percentages of observations between groups, χ^2 testing was used. Data are presented as mean with standard deviation (SD) or standard error (SE), unless otherwise specified. All statistics were performed in SPSS version 19 (SPSS Inc, Chicago, IL, USA). A *p* value <0.05 was considered statistically significant.