Health-Related Quality of Life of Patients with Tuberous Sclerosis Complex and Associated Manifestations

SP020

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INTRODUCTION

- Renal angiomyolipomas (rAMLs), epilepsy and subependymal giant cell astrocytoma (SEGA) are common manifestations of tuberous sclerosis complex (TSC)
  - rAML: observed in up to 85% of patients with TSC[1,2]
  - Epilepsy: observed in up to 93% of patients with TSC,[3] and
  - SEGA: observed in up to 20% of patients with TSC[4]
- TSC manifestations have a high disease burden
  - rAML: large rAMLs may impair kidney functioning possibly resulting in dialysis, kidney transplant, or nephrectomy
  - Epilepsy: seizures in TSC are associated with cognitive impairment[5,6] and substantial morbidity, including psychiatric and behavioral disorders, autism spectrum disorders, and attention deficit hyperactivity disorders[7,8]; over 60% of patients with TSC-epilepsy experience refractory seizures[9]
  - SEGA: tumor growth causes mental impairment, loss of vision, and increased seizure frequency which impact work opportunities and increase dependence on others
- The cumulative disease burden of TSC manifestations may result in reduced health-related quality of life (HRQoL) for the patients with TSC
- However, little is known on the HRQoL in patients with different TSC manifestations

OBJECTIVE

- The objective of the current study was to assess the HRQoL of patients with TSC who have associated rAML, epilepsy and/or SEGA manifestations

METHODS

Data source

- The study included patients with TSC managed from 1990-2012 at the University Medical Center Utrecht (UMCU), a major specialty center in the Netherlands for patients with kidney tumors
  - TSC, rAML, epilepsy, and SEGA-related data was extracted from the patients' medical charts
  - Patients' HRQoL was measured in 2012 via a generic Health Utility Index[10] (HUI)
  - All patients with TSC managed at the UMCU were invited via mail to fill out the HUI questionnaire (two versions were provided: a patient version and a caregiver version)
  - Response rate was 66% (242 respondents / 369 patients with TSC, with or without associated manifestations)
  - 38.4% questionnaires were filled by caregivers (for patients with intellectual disabilities)

Study design

- The study used a single-center retrospective cross-sectional study
- Index date = the date of the 2012 HUI assessment
- Patient characteristics, including TSC manifestations, were measured at the index date (when information was available) or at the most recent measurement prior to the index date

Study sample and cohorts

- All patients with complete HUI data and ≥1 TSC manifestation were included in the study (N=216)
- Patients were classified into cohorts based on the presence of associated rAML, epilepsy and/or SEGA manifestations at the time of the HUI assessment (only cohorts with >10 patients were reported in the stratified analyses)
  - TSC-rAML-epilepsy (N=113)
  - TSC-rAML only (N=42)
  - TSC-rAML-epilepsy-SEGA (N=33)
  - TSC-epilepsy only (N=18)
  - TSC-rAML-SEGA (N=6)
  - TSC-epilepsy-SEGA (N=4)
  - TSC – SEGA only (N=0)
- Additional subgroups of interest for the HUI analysis were defined based on patient characteristics (**Table 3**)

Health Utility Index (HUI)

- HUI[10,11] is a validated HRQoL tool that describes 8 dimensions of health status: vision, hearing, speech, ambulation/mobility, pain, dexterity, emotion and cognition (HUI version 3)
- Each health dimension has 5–6 levels. For example, the cognition dimension has 6 levels, with level 1 corresponding to *"Able to remember most things, think clearly and solve day to day problems"* and level 6 corresponding to *"Unable to remember anything at all, and unable to think or solve day to day problems."*
- HUI provides a score for each dimension of health (0–1 scale) and a HRQoL score for overall health (-0.371 to 1 scale)
  - Dimension-specific HRQoL scores were derived from the level of health for each dimension, with 0 corresponding to most disabled and 1 to perfect health. For example, for the cognition dimension, a score of 1 is attributed to level 1, 0.86 to level 2, 0.92 to level 3, 0.70 to level 4, 0.32 to level 5, and 0 to level 6
  - Overall HUI score was calculated by combining the dimension-specific HRQoL scores using the formula below. Note that a patient with a score of zero (most disabled) for all dimensions has an overall score of -0.371 (negative scores represent states worse than death; 0 represents death). Thus, the overall HUI score can be lower than all dimension-specific scores

$$\textit{HUI score} = (1.371 \times \textit{vision} \times \textit{hearing} \times \textit{speech} \times \textit{ambulation} \times \textit{dexterity} \times \textit{emotion} \times \textit{cognition} \times \textit{pain}) - 0.371$$

- Differences of ≥0.03 in mean overall HUI score are generally considered clinically relevant[11]
- Other studies have used the HUI score (**Table 1**)

Table 1. HUI version 3 in different populations (reference scores)

Age (years)	Population	Mean HUI (version 3)	Reference
18+	Patients with Alzheimer's disease	0.22	Neumann et al[12]
18+	Patients with rheumatoid arthritis	0.44	Kaplan et al[13]
–	Patients with chronic kidney disease stages 4 – 5	0.54–0.67	Gorodetskaya et al[14]
18+	Patients with difficult to control focal epilepsy investigated for epilepsy surgery	0.56–0.61	Wiebe et al 2002[15]
12+	Patients with both cancer and diabetes	0.67	Bowker et al[16]
65+	US general population*	0.70	Luo et al[17]
16+	Patients with temporal lobe epilepsy, candidates for TLE surgery	0.71	Wiebe et al 2001[18]
5+	Survivors of brain tumors in childhood assessed at study entry (2+ yrs post-tx), and 5 and 10 years after	0.77–0.88	Duckworth et al[19]
45–64	US general population*	0.78	Luo et al[17]
18–44	US general population*	0.86	Luo et al[17]

* Same HUI estimates were reported in the US Non-Black, Non-Hispanic population

Statistical analysis

- Patient demographic and clinical characteristics were reported for all cohorts with >10 subjects
- HUI was analyzed overall and by health dimension; HUI means and corresponding 95% confidence intervals (CIs) were reported

RESULTS

Patient characteristics

- Across the full study sample, 113 (52%) were male, median age was 39.0 years (92% adults), and all patients were Caucasian (results not shown in Table 2)
- Patients in the TSC-epilepsy only cohort appeared to be younger than patients in the other cohorts (80% vs. 0% children) and to include more males
- 58% of patients with ≥2 TSC manifestations lived in a group home
- *TSC2* mutations appeared to be associated with the presence of multiple TSC manifestations
- Comorbidities, particularly skin, skeletal, and cardiovascular disorders were common in all cohorts

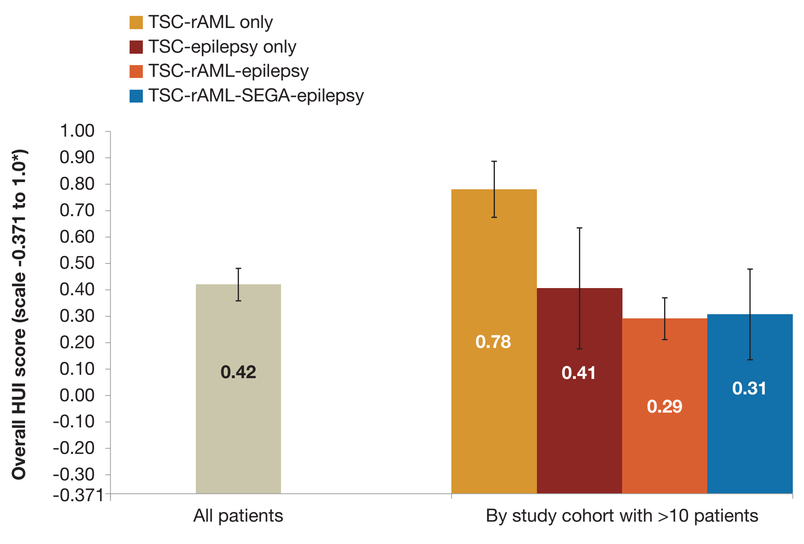
Table 2. Patient characteristics

Characteristics	*TSC* cohorts with > 10 patients			
	rAML only N=42	Epilepsy only N=18	rAML-epilepsy N=113	rAML-SEGA-epilepsy N=33
Males, n (%)	19 (45.2)	11 (61.1)	62 (54.9)	14 (42.4)
Age, mean ± SD [median]	43.2 ± 15.6 [40.5]	27.3 ± 9.2 [25.1]	39.9 ± 12.8 [40.0]	35.0 ± 9.3 [32.6]
<18 years	0 (0.0)	14 (77.8)	0 (0.0)	0 (0.0)
18-40 years	21 (50.0)	4 (22.2)	57 (50.4)	19 (57.6)
>40 years	21 (50.0)	0 (0.0)	56 (49.6)	14 (42.4)
Caucasian race, n (%)	42 (100.0)	18 (100.0)	113 (100.0)	33 (100.0)
Living arrangement, n (%)				
Independent	33 (78.6)	2 (11.1)	21 (18.6)	5 (15.2)
With caregiver	12 (28.6)	5 (27.8)	39 (34.5)	14 (42.4)
Group home	1 (2.4)	8 (44.4)	64 (56.6)	21 (63.6)
***TSC* mutations, n (%)**				
Had a test for gene mutations	37 (88.1)	17 (94.4)	107 (94.7)	31 (93.9)
TSC1 mutation	8 (19.0)	6 (33.3)	19 (16.8)	5 (15.2)
TSC2 mutation	11 (26.2)	7 (38.9)	48 (42.5)	17 (51.5)
Comorbidities, n (%)				
Skin disorders	36 (85.7)	14 (77.8)	95 (84.1)	28 (84.8)
Skeletal disorders	21 (50.0)	9 (50.0)	63 (55.8)	21 (63.6)
Cardiovascular conditions	17 (40.5)	6 (33.3)	66 (58.4)	16 (48.5)
Sleep disorders	4 (9.5)	1 (5.6)	15 (13.3)	3 (9.1)
Eye disorders	3 (7.1)	7 (38.9)	38 (33.6)	17 (51.5)

Overall HUI

- Patients with multiple TSC manifestations appeared to have lower overall HUI scores than those with a single rAML manifestation
- Epilepsy manifestations of TSC and epilepsy-associated conditions (paralysis, cognitive impairment, autism) appeared to be associated with the greatest burden on the patient's HRQoL vs. rAML only
- Patients with TSC-epilepsy (± rAML or SEGA) and prior use of antiepileptic drugs and patients with TSC-SEGA (± rAML or epilepsy) also had low overall HUI scores

Figure 1. Overall HUI, study sample and cohorts



* Please note scale of overall HUI (-0.371 to 1.0) is different than the scale of health-dimension specific HUIs (0 to 1); please see Methods for details.

Table 3. Overall HUI, subgroups

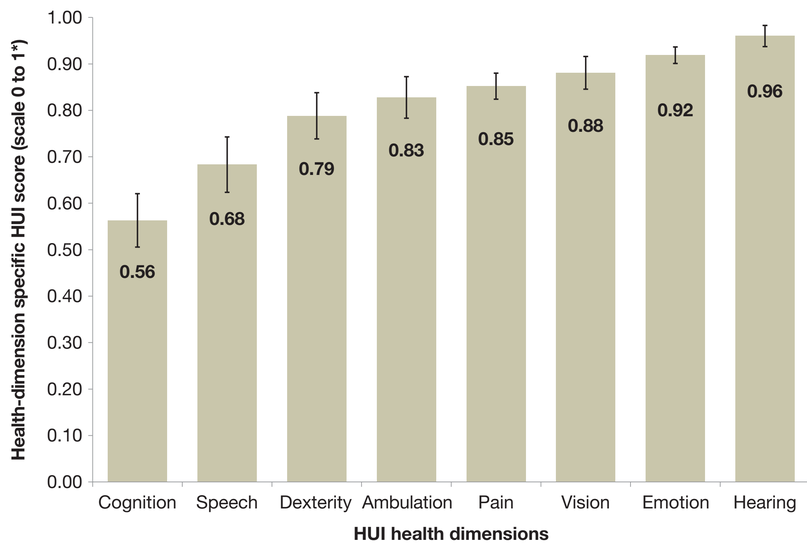
Subgroup	Subgroups size, N	Mean overall HUI score (95% CI)[1]
All patients with TSC-rAML (± epilepsy or SEGA)	194	0.42 (0.35 ; 0.48)
With rAML stages 0–2 (i.e., all rAMLs <3.5 cm)	120	0.47 (0.39 ; 0.55)
With rAML stages 3–6 (i.e., at least one rAML ≥3.5 cm)	74	0.33 (0.22 ; 0.44)
With prior kidney intervention[2]	75	0.41 (0.31 ; 0.52)
With eGFR≥30 mL/min/1.73msq[3]	188	0.41 (0.35 ; 0.48)
With anemia (Hb<8 g/dL)[3]	57	0.29 (0.17 ; 0.42)
All patients with TSC-epilepsy (± rAML or SEGA)	168	0.31 (0.25 ; 0.38)
With prior epilepsy surgery	9	0.57 (0.26 ; 0.88)
With prior use of antiepileptic drugs, but no epilepsy surgery	134	0.25 (0.18 ; 0.32)
With autism	36	0.25 (0.12 ; 0.37)
With paralysis	13	–0.15 (–0.33 ; 0.04)
With low or very low intelligence coefficient[4]	122	0.16 (0.09 ; 0.23)
All patients with TSC-SEGA (± rAML or epilepsy)	43	0.41 (0.27 ; 0.56)
With SEGA surgery[5]	9	0.57 (0.26 ; 0.88)

[1] The overall HUI score ranges from -0.371 to 1; [2] Transplant, nephrectomy, or embolization; [3] Before the HUI data collection; [4] By physician assessment; [5] For all patients the SEGA surgery occurred >1 year before.

Health-dimension specific HUIs

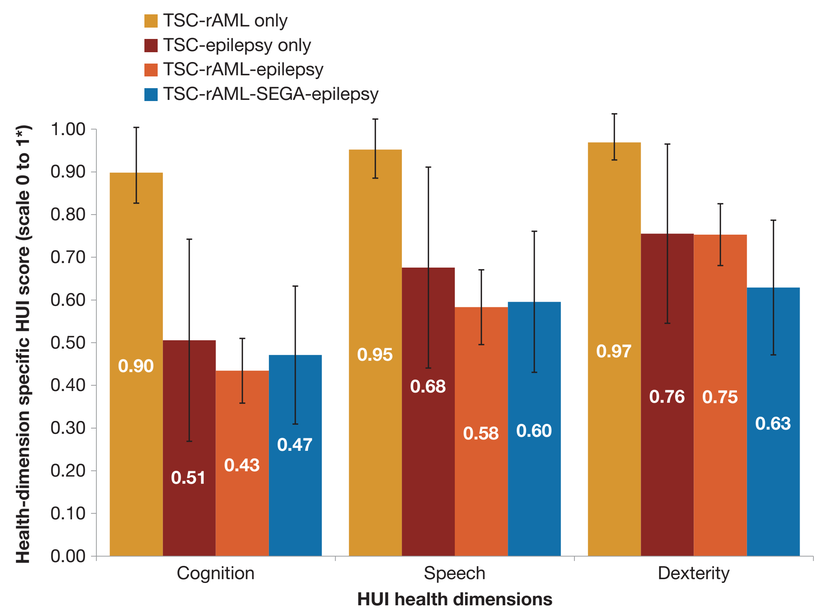
- Of the 8 health dimensions included in the HUI score, the top three that had the highest impact on the overall HUI score were cognition (mean dimension-specific score: 0.56; on a 0–1 scale), speech (0.68), and dexterity (0.79)
- Emotion and hearing dimensions appeared to have little impact on the overall HUI in this population (mean dimension-specific scores >0.90)
- HUI scores for cognition, speech and dexterity were lower for cohorts with epilepsy and/or SEGA manifestations compared with TSC-rAML only

Figure 2. Health-dimension specific HUIs, study sample



* Please note the scale of health-dimension specific HUIs (0 to 1) is different than the scale of overall HUI (-0.371 to 1.0); please see Methods for details.

Figure 3. Dimension-specific HUI, cohorts



* Please note the scale of health-dimension specific HUIs (0 to 1) is different than the scale of overall HUI (-0.371 to 1.0); please see Methods for details.

LIMITATIONS

- Some patients invited to participate in the HUI assessment were non-responders; however, these patients appeared to be similar in age, sex, living arrangement, TSC mutations, and most comorbidities
- Results may not be generalizable outside of the Netherlands

DISCUSSION AND CONCLUSIONS

- All TSC cohorts and subgroups investigated in this study, that involved epilepsy, appeared to have mean overall HUI scores below the reference score for the US in the general adult population and also below the HUI score previously reported for patients with cancer and diabetes or some forms of epilepsy without TSC
- Patients with ≥2 TSC manifestations had overall HUI scores below those previously observed in patients with advanced chronic kidney disease or rheumatoid arthritis
- Overall HUI scores for patients with both TSC and epilepsy were especially low, with the exception of the subgroup that had prior epilepsy surgery
- In TSC patients with epilepsy, the cognition health-dimension had the largest impact for patients' overall HRQoL
- Identifying treatments to delay or prevent the progression of TSC-related manifestations may improve the HRQoL of patients with TSC

Disclosures

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