

Title:

Quality of life in patients with Tuberous Sclerosis Complex (TSC)

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Abstract

Background: The quality of life (QoL) of patients with Tuberous Sclerosis Complex (TSC) has not been studied before. We aimed to investigate the impact of the disease on QoL. We studied the QoL of 91 TSC patients who have attended the Bath TSC clinic, UK over 6 months. QoL was evaluated using the PedsQL for children, and SF-36 for adults.

Results: Impaired QoL is found in all patients with TSC regardless of the presence of epilepsy and learning disabilities (LD). Total mean self-reported score for children was 71 out of 100, compared to a UK norm of 84, $p < 0.000$. The proxy mean score was 48, (UK norm 85, $p < 0.000$). Physical Functioning score for adults with TSC was 70, compared to a UK norm of 94, $p < 0.000$. The Social Functioning score for adults with TSC was 71, (UK norm 88, $p < 0.000$).

Conclusions: Impaired QoL is found in all patients with TSC regardless of the presence of epilepsy and learning disabilities. The psychosocial domain is most affected. The quality of life of children with TSC is lower than children who suffer from asthma, diabetes, cancer and inflammatory bowel disease.

To improve health related quality of life in TSC, a focus on patient's physical health, educational performances, and overall quality of life is crucial. In order to achieve this, coordinated medical care across disciplines, and psychosocial and social support is necessary.

Introduction

QoL is an important component in assessing the efficacy of treatment. QoL assessment in the clinical and research setting has become a significant outcome measure in determining response to medical interventions and the control of chronic conditions.

Tuberous Sclerosis Complex (TSC) is a chronic condition caused by mutations in the tumour suppressor genes *TSC1* and *TSC2*, located on chromosomes 9 and 16. (1, 2) The incidence has been estimated to be 1 per 5,800 live births. (3) The protein products of *TSC1* and *TSC2* (hamartin and tuberlin) function together within the cell. They have an inhibitory effect on the mammalian target of rapamycin (mTOR), a protein kinase that influences cell growth. (4) Mutation in either *TSC1* or *TSC2* leads to over-activation of the mTOR pathway and relatively uncontrolled cell growth. This, in turn, causes growth of benign tumours (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones. (5)

The central nervous system is most commonly involved in TSC. Epilepsy is a common presenting problem. Many patients go on to develop refractory epilepsy throughout life. Learning, behavioral and other neuropsychiatric issues have been encountered in TSC. (6, 7). Sub-ependymal giant cell astrocytomas (SEGAs) are seen in approximately 5% to 20% of patients with TSC. As they grow adjacent to the Foramen of Monro, they can cause clinical problems such as blocking the cerebrospinal fluid pathways within the ventricular system leading to obstructive hydrocephalus. (8)

Renal involvement in TSC is also potentially serious and very common. Angiomyolipomas (AML) is the leading cause of death.(9) The presenting features of AMLs are haematuria, pain, high blood pressure and renal failure.

Pulmonary lymphangiomyomatosis (LAM) occurs almost exclusively in female patients. They can present with progressive shortness of breath, recurrent pneumothoraces, and deterioration in lung function. (10)

The burden of the disease as a whole and the QoL of patients with TSC have not been studied before. QoL has been looked at as a secondary outcome in drug trials and surgical series. Krueger et al studied the efficacy of everolimus in 20 children with refractory epilepsy and TSC in an open label study. The secondary outcomes were the effect of everolimus on quality of life and behaviour. This is a selective group of children with refractory epilepsy due to TSC. (11)

Liang et al reported in a retrospective study the effect of epilepsy surgery on QoL of 25 children who had epilepsy surgery for intractable epilepsy. The quality of life profile of this group does not reflect the general TSC population as it is a selective group with intractable epilepsy who required surgery.(12)

We are conducting this study to investigate the impact of the disease on children and adults' QoL. The results of such a study may help clinicians and policy makers decide where best to focus efforts and resources to improve the quality of life of these patients.

Method

In this study, we investigated the QoL of 91 patients (35 children and 56 adults) with a definite diagnosis of TSC, as defined by the International Tuberos Sclerosis Complex Consensus Group(13) who have attended the Bath TS clinic from February 2014 to August 2014. None of the patients were excluded from this study.

QoL was evaluated using the Pediatric Quality of Life Inventory (PedsQL) for children.(14) Parents and the children were asked to complete the questionnaire during their clinic appointment at the TSC clinic in the presence of TS specialists. Parents completed the assessments for their children who were unable to complete due to learning disabilities (LDs). The SF-36 form was used to assess the quality of life of adults with TSC. The form was completed by parents or carers on behalf of those adults with learning disabilities.

This is a clinic cohort in which there was heterogeneity in terms of administered investigations. For example, not all patients were administered psychometric tests in a consistent fashion, but some tests were requested and administered when an initial clinical screen of abilities identified areas of concern. Patients were given the diagnosis of learning disability based on their abilities to understand new or complex information or to learn new skills, or their ability to cope or live independently, and with such inabilities having started before adulthood. Although these categorisations were made on the basis of clinical assessment rather than according to any measurement tool, they broadly concur with the definitions of learning disability

defined by the UK Department of Health(15). Ethical approval was not required as this assessment is being used as part of patient's routine care.

We have compared the results of this study with other chronic conditions including diabetes, asthma, cancer and inflammatory bowel disease. We have chosen these chronic condition because the same QoL tools have been used in these populations.

TSC with and without epilepsy population

These patients were categorized into this group during the recruitment at their clinic appointments between February 2014 to August 2014. TSC patients without epilepsy were defined as patients who have never had epilepsy.

TSC with and without learning disabilities

We divided this cohort into two groups: those with and those without learning disabilities. Patients were given these diagnoses of learning disability based on their abilities to understand new or complex information or to learn new skills, or their ability to cope or live independently, and with such inabilities having started before adulthood. Although these categorizations were made on the basis of clinical assessment rather than according to any measurement tool, they broadly concur with the definition of learning disability defined by the UK department of Health(15).

Statistical analysis

The unpaired t test was used to compare the means of different domains of PedQL and SF36 of patients with TSC compared with the means of the normal population, and patients with other conditions. This was also used to compare the means of children and adults with TSC with and without epilepsy and learning disabilities.

Paired t test was used to compare the means of QoL of children's self reports and their parents' reports. We have used parametric analysis because the data is normally distributed.

Rational for the choice of the assessment tools used in the present study

There are several tools that have been used in assessing children's quality of life. A systematic review identified 43 quality of life assessment measures, disease specific and generic, and concluded that the PedsQL is the most promising tool (16).

PedsQL is a short, standardised, generic assessment tool which methodically evaluates patients' and parents' perceptions of health related quality of life in paediatric patients with chronic conditions. PedsQL is more acceptable than other assessment measures because of its brevity, reliability, validity, availability of age appropriate versions and equivalent forms for child and parent. In addition, it has a core and modular design which makes it flexible for use in a range of research and clinical settings for children with chronic conditions (14).

The PedsQL was originally derived from data collected from a group of US children with cancer, and their parents, at different stages of treatment. The original version of PedsQL has been through several improvements to achieve a more sensitive rating scale, a wider age range, and to match the core dimensions defined by WHO. In this study, we used the UK version PedsQL 4.0. This version has had its performance assessed on a group of healthy UK children, and children with chronic conditions and their parents. It has been shown that the UK-English version of

PedsQL™ performance is as good as the original PedsQL™ and it has been recommended for assessment of paediatric health related quality of life in the UK (17).

The child and parent reports of the PedsQL 4.0 Generic Core Scales are for 3 age groups including children aged 5-7, 8-12 and 13 to 18. It is composed of 23 items comprising 4 dimensions: physical, emotional, social and school functioning. The physical domain has 8 items, emotional 5, social 5 and school 5. The physical health summary score is calculated as the sum of the items in the physical domain over the number of items. The Psychosocial Health Summary Score is calculated as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales.

In this study, we used SF36v2 for adults with TSC with and without learning disabilities (LD). This tool was initially used in the US in a health insurance experiment. It was then translated into more than 100 languages and used in many countries. It is a generic, multipurpose, short survey, with 36 questions that assess health status, and it has been proven to be useful in general and specific populations(18). Studies have shown that proxy assessment for SF36 is reliable and valid(19). The SF-36 contains 36 item scales, which measure eight domains of health status including: physical functioning (10 items); physical role limitations (four items); bodily pain (two items); general health (five items); energy/vitality (four items); social functioning (two items); emotional role limitations (three items) and mental health (five items). A scoring algorithm is used to convert the raw scores into the eight dimensions listed above. The scores are transformed to range from zero where

the respondent has the worst possible health to 100 where the respondent is in the best possible health (20).

We compared the quality of life of our cohort of TSC patients with the healthy population. Upton et al recruited children from 23 schools in South Wales to obtain a baseline quality of life for a healthy population. 1034 children self-completed the QOL questionnaire and 665 parents completed proxy reports. The psychometric properties of this version were similar to those reported for the original US version of PedsQL. Internal reliability exceeded 0.70 for all proxy and self-report sub-scales. Discriminant validity was established for proxy and self-report with higher HRQL being reported for healthy children than those with health problems. Sex differences were noted on the emotional functioning subscale, with females reporting lower HRQL than males. Proxy and self-report correlation was higher for children with health problems than for healthy children(17).

The normative data for SF36 which is used in this study is derived from the Oxford Healthy Life Survey 1992. The Oxford Healthy Life Survey was conducted in Central England. The questionnaire was sent by post to 13800 randomly selected subjects between the ages of 18–64 inclusive. The individuals were identified through their General Practice. The survey achieved a response rate of 64.4%. Internal consistency of the different dimensions of the questionnaire were found to be high(18).

Results

The QoL of 91 patients was assessed. There were 35 children and 56 adults. The median age of the children was 12 and of the adults was 34. There was no gender difference amongst the adults and the male to female ratio in children was 19/16.

43 out of 56 adults had epilepsy, of whom 35 had learning disabilities. All patients with LD had epilepsy. 29 out of 35 children had epilepsy, of whom 19 had learning disabilities. Again, all children with LD had epilepsy.

21 out of 56 adults had no learning disabilities and completed the self reported questionnaire. The proxy reported questionnaire were completed by parents and carers for the 35 adults with learning disabilities. 16 out of 35 children did not have learning disabilities and completed the self reported QoL questionnaire. The 19 children who had learning disabilities were unable to complete the self QoL questionnaire. Parents completed the proxy questionnaire for all the 35 children.

Comparison to healthy control children (see table 1)

In comparison with the sample of healthy children, there is a significant difference in the child self-report and proxy-report in the total scale scores. Both the self and proxy reports on psychosocial domains were significantly different from the healthy population. In addition, the children and their parents reported a significant difference of QoL of physical domain compared with the healthy population. All the other self and proxy reported QoL domains were significantly lower than the healthy population except the self reported emotional domain. This remained insignificant after adjusting for epilepsy and learning disabilities.

Comparison to children with chronic conditions(17) (see table 2)

TSC and diabetes, cancer and IBD (Inflammatory Bowel Disease)

Both children with TSC and their parents, reported a significantly worse quality of life than was reported by children with diabetes, cancer or IBD, and their parents.

TSC and asthma

In comparison to children with asthma, the self report for total scores and the psychological scores showed an insignificant difference.

QoL in adults with TSC and healthy population(20) (see table 3)

Adult patients with TSC reported a poorer quality of life compared to the healthy population. Regardless of the presence of learning disabilities and epilepsy, there is a highly significant difference between all the domains of SF36 in TSC patients and the healthy population, apart from the mental health domain.

Discussion

This is the first study investigating the quality of life of patients with TSC. We note that quality of life is significantly reduced in both adults and children with TSC, compared with the healthy population. The psychosocial domain showed the biggest reduction, compared to the other domains of quality of life. It also highlighted that

children and adults with TSC without epilepsy and learning disabilities, report a poorer QoL. Pain was reported less in adults with LD than in adults with normal intellect. The quality of life of children with TSC was reported to be lower than children who suffer from asthma, diabetes, cancer and IBD.

There are limitations with this study. The study was based on a clinic population. Supra-regional specialist clinics tend to care for patients who are more severely affected by the disease, and we would therefore anticipate that this cohort may report a poorer quality of life, due to a greater severity of medical issues and comorbid factors than the overall population of patients with TSC. The gender balance and prevalence of learning disabilities in our clinic cohort, however, was similar to previously reported population based TSC cohorts, suggesting that this clinic population was not grossly dissimilar from the TSC population at large(21). Another limitation is that the quality of life questionnaires for patients with severe learning disabilities were completed by parents and carers. This method of quality of life assessment is less reliable than self-reported outcomes, but it is the only practicable method of assessment in people with learning disability, and it remains of interest.

Regarding the pain score, the higher the score, the less pain patients are believed to experience. The total mean score for body pain for patients with learning disabilities was 81 out of 100. Whilst the mean score for adults without learning disabilities was 62, and is 87 for the general population. This tells us that carers and parents of adults with TSC with learning disabilities report less pain compared to adults with TSC who have no learning disabilities. This makes the reliability of parents and

carers reports on pain questionable. Clinicians tend to rely on parents and carers reports of pain. Some of the surveillance monitoring checks are based on the presence of pain in patients with TSC. For example, SEGA complications/growth such as hydrocephalus can present with headaches, and angiomyolipoma complications such as bleeding can manifest as loin pain. We may have to be cautious when relying on proxy reports for pain. One could argue that individuals with learning disabilities should be screened more carefully, as these complications can not be easily detected based on history. Perhaps more frequent monitoring by imaging could be offered to this group. We know from experience, that individuals with TSC and learning disabilities are more likely to develop fatal complications compared to those without learning disabilities(9).

In this study, 76% of adults had epilepsy, and 82% of the children had epilepsy. One could argue that the quality of life of these patients in this cohort is worse than the healthy population because of their epilepsy, and not because of TSC as a whole. Epilepsy is a significant morbidity and can have a significant impact on patient's quality of life(22). However, in our study, patients without epilepsy also showed poorer QoL scores compared with the general population. In this study, 62% of adults and 54% of children had learning disabilities. The presence of learning disabilities is another comorbidity which can inversely affect an individual's quality of life(23). However, children and adults without learning disabilities also reported a poorer quality of life compared to the healthy UK population. This study highlights an interesting point that children and adults with TSC without epilepsy and learning disabilities, report a poorer QoL compared with the healthy population. It is not clear as to why their QoL remains poor when adjusted for epilepsy and LD. It is possible

that there are other comorbidities impacting their quality of life and this will require further study.

Both the self and proxy reported scores for children with TSC were significantly lower than the general population. Proxy report by parents for the psychosocial domain was 25% worse than the self report. Despite the difference between self reported and proxy scores, they still appear reliable, as they both have reported a significantly poorer QoL compared with the general population. This is similar to other studies that often report lower quality of life by proxy reports than by self report(24). Higher agreement between self and proxy reports is seen for observable physical aspects of QoL, compared to emotional or social aspects(16).

We report that that the point difference in quality of life domains, especially the social, in both children and adults, compares similarly with the general population. The self reported total mean score for social functioning in adults with TSC was 80, and is 88 in the general population (point difference 8). The self reported total mean score for social functioning in children with TSC was 73, and is 88 in the general population (point difference 15). One explanation for adults reporting better social scores than children, is that the adults have learned to cope with TSC and have learnt strategies to help minimise the burden of the disease on their psychology. We noted that the parents reported worse psychosocial domain scores than their children. Having said that, the quality of life assessment of children and adults were performed using two different assessment tools (PedsQL for children and SF36 for adults) and therefore it may not be reliable to compare the results of these two QoL assessment tools.

This study has also highlighted that the burden of TSC on patients is more than the burden of other medical conditions; asthma, diabetes, cancer and inflammatory bowel disease. This is an important finding, as a lot of patients with TSC do not have access to appropriate treatment. For example, Neuropsychology assessments and interventions play a crucial part in the management of TSC patients, but many do not have access to these services. We have seen in this study that the psychosocial burden is significant, and therefore, it is important that all patients are offered this neuropsychology assessment as early as possible. It would therefore be beneficial to have a psychologist linked to TSC services to give easier access.

Conclusion

QoL is significantly reduced in adults and children with TSC compared with the normal population. The psychosocial domain is most affected. Although small in number, all the children and adults in our study who did not have epilepsy or learning disabilities, reported a low quality of life. Pain was reported less in adults with LD than normal intellect but this may reflect the inaccuracy of proxy assessment of pain in this population. Complication surveillance for SEGA (Subependymal giant cell astrocytoma) and AML (angiomyolipoma) lesions should be assessed carefully, especially in patients with LD, as pain report by proxy may be unreliable. To improve health related quality of life in TSC, a focus on patient's physical health, educational performances, and overall quality of life is crucial. In order to achieve this,

coordinated medical care across disciplines and psychosocial and social support is necessary. TSC patients should be managed with a multidisciplinary approach, as there are several comorbidities which are interconnected. Further research is required to discover hidden burden in this population.

Abbreviation

QoL: quality of life

TSC: Tuberous Sclerosis Complex

LD: Learning disabilities

mTOR: mammalian target of rapamycin

SEGA: Sub-ependymal giant cell astrocytomas

AML: Angiomyolipomas

LAM: lymphangioleiomyomatosis

IBD: Inflammatory Bowel Disease

Table 1: shows the total mean and all different domains of PedsQL for children with TSC

PedsQL scales	Healthy population N= 1698	TSC population N=35		TSC without epilepsy N=6		TSC with epilepsy N=29		TSC without learning disabilities N=16		TSC with learning disabilities N=19		TSC without epilepsy and learning disabilities N=6	
	Mean (SD)	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value
<i>Child self-report</i>	<i>n=1033</i>	<i>n=16</i>		<i>n=6</i>		<i>n=10</i>		<i>n=16</i>		<i>n=0</i>		<i>n=6</i>	
Total score	84 (11)	71 (20)	<0.0001	79 (17)	0.324	67 (21)	<0.0001	71 (21)	<0.0001	NA	NA	79 (17)	0.324
Psychosocial	82 (13)	67 (22)	<0.0001	74 (17)	0.157	62 (24)	<0.0001	67 (23)	<0.0001	NA	NA	74 (17)	0.157
Physical	88 (11)	78 (21)	0.0003	88 (19)	0.994	72 (20)	<0.0001	77 (21)	0.0001	NA	NA	88 (19)	0.994
School	79 (15)	60 (28)	<0.0001	63 (36)	0.018	58 (25)	<0.0001	60 (29)	<0.0001	NA	NA	63 (36)	0.018
Social	88 (16)	72 (27)	<0.0001	81 (22)	0.314	67 (29)	<0.0001	73 (27)	0.0007	NA	NA	81 (22)	0.314
Emotional	78 (17)	71 (19)	0.090	78 (13)	0.992	68 (22)	0.050	71 (20)	0.098	NA	NA	78 (13)	0.992
<i>Parent proxy-report</i>	<i>n=665</i>	<i>n=35</i>		<i>n=6</i>		<i>n=29</i>		<i>n=16</i>		<i>n=19</i>		<i>n=6</i>	
Total scores	85 (11)	48 (24)	<0.0001	74 (18)	0.027	43 (21)	<0.0001	65 (22)	<0.0001	33 (14)	<0.0001	74 (18)	0.027
Psychosocial	82 (12)	42 (21)	<0.0001	67 (20)	0.004	36 (17)	<0.0001	54 (22)	<0.0001	31 (11)	<0.0001	67 (20)	0.004
Physical	89 (12)	56 (28)	<0.0001	85 (19)	0.413	50 (27)	<0.0001	73 (26)	<0.0001	39 (22)	<0.0001	85 (19)	0.413
School	82 (16)	41 (26)	<0.0001	67 (25)	0.024	36 (24)	<0.0001	59 (25)	<0.0001	27 (15)	<0.0001	67 (25)	0.024
Social	87 (15)	41(28)	<0.0001	71 (23)	0.012	35 (26)	<0.0001	57 (29)	<0.0001	29 (18)	<0.0001	71 (23)	0.012
Emotional	78 (15)	47 (24)	<0.0001	72 (16)	0.304	42 (23)	<0.0001	60 (22)	<0.0001	35 (18)	<0.0001	72 (16)	0.304

* compares the means with healthy population.

PedsQL scales	Healthy population N= 1698	TSC population N=35		Diabetes N=124		Cancer N=66		IBD N=76		Asthma N=99	
	Mean (SD)	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value	Mean (SD)	*P value
<i>Child self-report</i>	<i>n=1033</i>	<i>n=16</i>		<i>n=124</i>		<i>n=66</i>		<i>n=76</i>		<i>n=99</i>	
Total score	84 (11)	71 (20)	<0.0001	82(12)	0.002	76(15)	0.04	74(14)	0.50	75(16)	0.38
Psychosocial	82 (13)	67 (22)	<0.0001	81(13)	0.000	74(15)	0.67	74(14)	0.10	75(17)	=0.08
<i>Parent proxy-report</i>	<i>n=665</i>	<i>n=35</i>		<i>n=103</i>		<i>n=21</i>		<i>n=67</i>		<i>n=74</i>	
Total scores	85 (11)	48 (24)	<0.0001	77(12)	<0.000	71(17)	<0.000	73(17)	<0.000	72(17)	<0.000
Psychosocial	82 (12)	42 (21)	<0.0001	75(13)	<0.000	68(17)	<0.000	73(17)	<0.000	71(17)	<0.000

Table 2 shows the total mean and psychosocial domains of PedsQL for children with TSC and other conditions

Table 3: shows the total mean and all different domains of SF36 for adults with TSC

SF36 scales	healthy population	TSC N=56		TSC patients without epilepsy N=13		TSC patients with epilepsy N=43		TSC patients without learning disabilities N=21		TSC patients with learning disabilities N=35		TSC patients without epilepsy and learning disabilities N=13	
	Mean (SD)	Mean (SD)	*P values	Mean (SD)	*P values	Mean (SD)	*P values	Mean (SD)	*P values	Mean (SD)	*P values	Mean (SD)	*P values
Physical Functioning n=4962	94 (12)	70 (33)	<0.0001	78 (34)	<0.0001	67 (33)	<0.0001	81 (31)	<0.0001	62 (33)	<0.0001	78 (34)	<0.0001
Role Physical n=5052	93 (13)	72 (36)	<0.0001	83 (34)	<0.0001	69 (36)	<0.0001	79 (35)	<0.0001	67 (36)	<0.0001	83 (34)	<0.0001
Body Pain n=5078	87 (16)	74 (29)	<0.0001	66 (35)	<0.0001	77 (27)	<0.0001	62 (34)	<0.0001	81 (24)	0.06	66 (35)	<0.0001
General Health n=4999	78 (15)	68 (21)	<0.0001	67 (29)	<0.0001	69 (19)	<0.0001	68 (27)	0.005	68 (18)	<0.0002	67 (29)	<0.0001
Vitality n=5076	62 (17)	57 (21)	0.03	57 (28)	0.03	58 (19)	0.03	56 (25)	0.090	58 (19)	0.15	57 (28)	0.03
Social Functioning n=5069	88 (18)	71 (27)	<0.0001	80 (26)	<0.0001	69 (28)	<0.0001	75 (26)	0.0009	68 (28)	<0.0001	80 (26)	<0.0001
Role Emotion n=5058	89 (16)	74 (32)	<0.0001	79 (28)	<0.0001	73 (33)	<0.0001	75 (30)	<0.0001	73 (34)	<0.0001	79 (28)	<0.0001
Mental Health n=5073	75 (16)	71 (15)	0.06	71 (18)	0.06	71 (14)	0.06	69 (19)	0.100	72 (12)	0.26	71 (18)	0.06

* compares the means with healthy population.

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