ORIGINAL RESEARCH

Description of a multidisciplinary model of care in a French cohort of adult patients with tuberous sclerosis complex

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ABSTRACT

Background Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder. Due to the various manifestations of TSC and their potential complications, a multidisciplinary care approach is recommended by consensus guidelines.

Objectives Our study aimed to give a complete description of our TSC adult cohort and to evaluate the multidisciplinary and interdisciplinary management model.

Methods Data on each adult patient diagnosed with TSC, including disease manifestations, interventions and outcomes, were collected at baseline and updated annually. A multidisciplinary TSC approach with all the recommended explorations was carried out annually.

Results 90 patients were enrolled in Centre Hospitalier Universitaire de Bordeaux, between January 2000 and September 2018. Median age of patients at inclusion was 37 years (range, 27–47) and 20 years old at diagnosis of TSC. Regarding the occurrence of TSC manifestations, 97% of the patients had cutaneous lesions, 89% had neurological manifestations, 83% had renal manifestations and 100% had dental lesions with pits. More than half the patients had sclerotic bone lesions (68%), TSC-associated neuropsychiatric disorders (64%) and lymphangioleiomyomatosis (59%). A TSC multidisciplinary approach was developed including a global follow-up and an evaluation of TSC targeting organs, according to the recommendations. A satisfaction survey revealed global and entire satisfaction of patients with TSC.

Conclusion We obtained an accurate description of a cohort of adult patients with TSC. Our multidisciplinary approach model allowed us to provide optimal management of patients with TSC with a high level of patient satisfaction.

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystemic disorder.[1–3] TSC has a prevalence of 1/20 000 and an incidence of 1/6000–10 000 live births, with no difference between ethnic groups or genders.[4 5] TSC manifests with the formation of hamartomas in different organs, including the central nervous system, skin, kidneys, lungs and heart.[1] This damage is caused by inactivating pathogenic variants in either the TSC1 or the TSC2 gene. Pathogenic variants in TSC1 or TSC2 lead to hyperactivation of the mammalian target of rapamycin (mTOR) signalling pathway, with a consequent deregulation of cell growth and the development of hamartomas.[6 7] Diagnosis is based on the presence of a genetic mutation in the hamartin protein code by TSC1 or in the tuberin protein code by TSC2,[8 9] and/or on specific clinical signs of TSC as published in the latest recommendations.[10] Tumours may develop throughout life. A patient may therefore develop separate tumours throughout life, either before birth, during early childhood and later in adulthood. Most of them are benign hamartomas, but they may cause life-threatening conditions, such as bleeding events or organ failure including brain, kidneys and lungs.[11–13] Lifelong monitoring is needed in order to understand the impact of this disease. However, the clinical manifestations of TSC are highly variable, ranging from a milder form (such as a single manifestation of TSC) to severe disease.[14] Because of these various manifestations with potential complications that may evolve over patient's lifetime, the expertise of different specialties is recommended to provide efficient care for patients with TSC.[10 15] The use of multidisciplinary teams (MDT) has been demonstrated as effective for patients, resulting in an improvement in patient care and its outcomes, for several complex diseases, and more recently for TSC.[16] In 2015, a multidisciplinary approach was applied in our centre, dedicated to adult patients with TSC. Our study aims to give a complete description of our TSC adult cohort and to evaluate the multidisciplinary and interdisciplinary management model. The secondary objective was to assess the quality of life of patients and families of patients with TSC.

MATERIALS AND METHODS

Population

Patients older than 16 years old with TSC and followed in Centre Hospitalier Universitaire (CHU) de Bordeaux between January 2000 and September 2018 were included in the registry. The diagnosis of TSC is based on international recommendations using clinical or genetic criteria.[10] Patients had to have an abdominal triphasic CT scan. Data were retrieved from hospital discharge files, clinical

records, clinic visits, electronic medical records and patient surveys.

TSC day

Since 2015, we have developed an interdisciplinary and multidisciplinary TSC day in our centre. During the day, patients had annually a clinical evaluation with a nephrologist, neurologist, dentist, ophthalmologist and psychologist. In addition to clinical and dermatological examinations, they had a body tomography. Lung function was assessed based on pulmonary function tests and a 6 min walk test. Cardiac function was tested with a 12-derivation ECG, and if any electrophysiological abnormality was observed a transthoracic echocardiogram was carried out. A blood test was performed to determine blood urea, creatine and blood count. Glomerular filtration rate (GFR) was estimated by Chronic Kidney Disease-Epidemiology Collaboration equation. Urinalysis with proteinuria, haematuria and cytobacteriological testing was also carried out. All the patients and their families completed surveys to assess their quality of life with the 36-Item Short Form Health Survey score.[17] This general survey enabled us to assess patients' physical functioning, physical limitations, pains, general health, emotional well-being, emotional limitations, social function and energy. Each item was scored on a 0–100 range. The lowest and highest scores were 0 and 100, respectively. Two composite scores were produced from these results: the physical health composite score and the mental health composite score. Anxiety was measured by the Beck Anxiety Inventory and depression by the Beck Depression Inventory. The intellectual impairment was evaluated by the Montreal Cognitive Assessment (MoCA). The burden of the family was evaluated by Zarit Burden Interview. An electronic medical record was structured prospectively to collect information on patients and the full description of the disease.

Imaging analysis

Images were blind reviewed by two radiologists. To avoid any recognition bias, the studies were presented in a random order. All imaging investigation data were assessed on a picture archiving and communication system station (DXMMTM Medasys Digital System, Norcross, GA). Undetermined measures were excluded for this criterion.

Definition

We used the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference for the diagnostic and for the management of TSC.[10] The diagnosis of angiomyolipomas (AML) was made on radiological characteristics by imaging explorations (usually ultrasound, CT or MRI). TSC-associated neuropsychiatric disorders (TAND) are defined by a wide range of cognitive, behavioural and psychiatric manifestations associated with TSC.

Evaluation of a multidisciplinary model of care

We compared the management of patients with TSC to the management and monitoring rate of international recommendations.[10] In order to also have an evaluation by the patients a specific patient satisfaction survey was also delivered to enable us to adapt and improve the quality of the TSC day.

Statistical analysis

Data processing was carried out in two stages: description and analysis.

Quantitative variables were described by combining means and SDs, while qualitative variables were described by relative numbers and numbers.

The choice of tests to be carried out depended on the nature of the data, with the comparison of two qualitative variables managed by χ^2 test or Fisher's test. The comparison of a binary qualitative variable against a quantitative one was managed by the Student's t-test, Welch's test and Wilcoxon-Mann-Whitney test. To compare a qualitative variable against a quantitative variable, we used analysis of variance or Kruskal-Wallis test. The comparison of two quantitative variables was done by Pearson correlation.

The tests were selected in accordance with their application conditions. Data management was done via Excel table, description and analyses were done using R software (V.3.6.0).

RESULTS

Patients and TSC manifestations

The demographic characteristics of patients are described in table 1. Study participants comprised 90 patients with TSC (42 (47%) males, 48 (53%) females) with a mean age of 42.75 years. Genetic testing results, including TSC1 and TSC2 sequencing, were available for 25 patients: 8 (32%) had a mutation in TSC1; 10 (40%) in TSC2; and 7 (28%) had no mutation identified. The initial presentation for the diagnosis was mostly neurological (53%). However, the initial mode of discovery differed depending on onset age. If the diagnoses were made in childhood, the initial presentation was neurological, whereas in adulthood, the diagnosis was mainly based on cutaneous signs (online supplementary data figure 1). TSC manifestations in our cohort are described in table 1, with the following distribution: 97% of the patients had cutaneous lesions, 89% had neurological manifestations, 83% had renal manifestations and 100% had dental lesions with pits. More than half the patients had sclerotic bone lesions (68%), TAND (64%) and lymphangioleiomyomatosis (59%).

Neurological manifestations

Neurological manifestations were present in 89% of patients with 17% having West syndrome in childhood and 67% having epilepsy (table 2).

Tubers were present in 81% of patients. Patients presented an average of 12.3±10.1 tubers. Tubers were located predominantly in the frontal lobe, parietal lobe, temporal lobe, occipital lobe and the infratentorial region. Subependymal nodules were observed in 73% of patients and subependymal giant cell astrocytomas (SEGA) in 14% of patients (78% of them had had surgical treatment).

TAND manifestations

Depression was detected in 39% of patients, and moderate to high anxiety in 22% of patients, with an over-representation for patients with a history of psychological disorders. MoCA was less than 26/30 in 35% of patients which differed from the intellectual impairment (54%) in our cohort (online supplementary data table 1).

Renal manifestations

The renal manifestations are described in table 3. Eighty-three per cent of patients had renal manifestations (AML, cyst or chronic kidney disease) related to TSC. The average GFR was 102.2±41.3 mL/min/1.73 m^2 with 31% of patients with at least chronic kidney disease stage 3. Among these patients, 6% were

Table 1 Demographic characteristics of patients with TSC

Characteristics	Value (%)	n
Sex		
Female	48 (53)	90
Male	42 (47)	90
Age	37 [27; 47]	90
Genetic mutation		
TSC1	12 (13)	90
TSC2	11 (12)	90
Not found	9 (11)	90
Unknown	58 (64)	90
Education level		
Specialised institute	25 (38)	65
Primary school	5 (8)	65
College	22 (34)	65
Graduate school	11 (17)	65
Have already worked		
No	23 (31)	74
Yes	51 (69)	74
Work currently	34 (67)	51
Need for institution		
Yes	29 (39)	74
No	45 (61)	74
Lifestyle		
Single	47 (59)	79
In couple	32 (41)	79
Children		
Yes	28 (37)	76
n	1.6±0.9	28
No	48 (63)	76
Affected organs		
Brain	70 (89)	79
TAND	42 (64)	66
Kidney	59 (83)	71
Skin	63 (97)	65
Lung	33 (59)	56
Heart	13 (23)	56
Teeth	42 (100)	42
Eyes	6 (13)	45
Bones	34 (68)	59

TAND, TSC-associated neuropsychiatric disorder; TSC, tuberous sclerosis complex.

dialysed and 12% had a kidney transplantation. Twenty-two per cent of patients presented hypertension treated with 1.9±1.3 antihypertensive drugs, such as renin-angiotensin-aldosterone system inhibitors (78%). Proteinuria and haematuria were detected in 21% and 17% of patients, respectively. AMLs were found in 70% of patients with a bilateral topography in 91% of cases. AMLs were greater than 4 cm in 42% of cases. Fifty-nine per cent of patients had renal cysts. An association between AMLs and cysts was observed in 61% of patients. AMLs were responsible for haemorrhage in 9% of patients. Preventive treatment by arterial embolisation was performed in 24% of patients.

Pulmonary manifestations

Pulmonary involvement was present in 56%. Only 6% of patients reported dyspnoea. A medical history of pneumothorax was found in 10% of patients. Pulmonary function tests showed that 7% and 15% of patients had obstructive respiratory failure or restrictive respiratory failure, respectively (table 4).

Table 2 Description of neurological lesions

Neurological manifestations	Value (%)	n
Epilepsy	51 (67)	76
Treated	41 (80)	51
Active	21 (41)	51
Treatment, n		
Vagus nerve stimulation	2 (4)	51
Surgery for epilepsy	0 (0)	51
History of West syndrome	11 (17)	66
Tubers	52 (81)	52
n	10 [4; 16]	52
Frontal lobe	4 [2; 7]	52
Temporal lobe	2 [1; 5]	52
Parietal lobe	2 [1; 7]	52
Occipital lobe	1 [0; 5]	52
Infratentorial region	0 [0; 1]	52
Subependymal nodules	47 (73)	64
Subependymal giant cell astrocytoma	9 (14)	63
Size (mm)	16.7±6.2	
Surgery	7 (78)	9
Hydrocephaly	3 (6)	46
White matter abnormalities	29 (63)	46
White matter cyst	10 (22)	46

Dermatological manifestations

Angiofibromas (92%) were the main lesion of cutaneous involvement in our TSC cohort (table 4). Other lesions are reported in table 4.

Oral manifestations

The oral manifestations are described in table 4. All patients presented dental manifestations with the characteristic pit lesions (100%). 24.6±22.8 pits were found in the maxillary teeth (5.80±1.93 *per* affected tooth, on average). Mandibular teeth were less affected, with 15.4±9.1 pits and 5.3±2.4 *per* affected tooth (table 4). Oral fibromas affected 64% of patients.

Other manifestations of TSC

Sixty-eight per cent of patients had sclerotic bone lesions. These were mostly found in the spine. Arrhythmias and conduction defects were observed in 8% and 15% of patients, respectively. Cardiac rhabdomyoma was present in 13% of patients (table 4).

Quality of life

An evaluation of the patient's quality of life had been performed with a specific survey on 29 patients. The most affected variable was patient's energy (48.62%). Health status was evaluated at 57.76% by the patients. Some variables were only slightly affected, physical function in particular (82%) (figure 1 and online supplementary data table 2).

The assessment of physical health and mental health indicated considerable deterioration (47.52% and 43.46%, respectively).

Similarly, an evaluation of the patient's family's quality of life had been performed with a dedicated survey. The results were similar to those found for patients, for each variable (physical health (51.98%) and mental health (43.17%)).

No significant difference was observed either in the overall quality of life or in all the variables, between patients and family members caring for patients (online supplementary data figure 2).

Table 3 Description of nephrological parameters and lesions

Nephrological damage	Value (%)	n
eGFR (mL/min/1.73 m^2)	102.2±41.3	42
CKD stage I	29 (57)	51
CKD stage II	6 (12)	51
CKD stage III	2 (4)	51
CKD stage IV	4 (8)	51
CKD stage V	1 (2)	51
Dialysis	3 (6)	51
Renal transplant	6 (12)	51
Haematuria	7 (17)	41
Proteinuria	9 (21)	43
(mg/mmol)	199.2±388.0	
Hypertension	18 (22)	81
Treatment, n	1.9±1.3	
ACE inhibitor/AIIRAs	14 (17)	81
Right kidney size (mm)	120.6±31.4	53
Left kidney size (mm)	125.6±26.9	53
Angiomyolipoma	45 (70)	64
Bilateral	32 (91)	35
Number <3	8 (20)	40
Number between 3 and 5	8 (20)	40
Number between 6 and 10	0 (0)	40
Number >10	24 (60)	40
Size of the biggest (mm)	41.0±39.7	35
History of haemorrhage	4 (9)	45
History of embolisation	11 (24)	45
History of surgery for haemorrhage	5 (11)	45
Indication of mTORi for AML	10 (22)	45
Kidney cysts	36 (59)	61
Number <3	14 (41)	34
Number between 3 and 5	9 (26)	34
Number between 6 and 10	2 (6)	34
Number >10	9 (26)	34
Kidney cancer	4 (7)	58

AIIRA, angiotensin II receptor antagonist; AML, angiomyolipoma; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor.

Table 4 Description of other parameters

Characteristics	Value (%)	n
Pulmonary disease	33 (59)	56
Dyspnoea	3 (6)	50
Pneumothorax	5 (10)	50
LAM	27 (51)	53
Pulmonary cyst	28 (56)	50
Obstructive pulmonary disease	3 (7)	40
Restrictive pulmonary disease	6 (15)	40
Pulmonary function test		
FEV_1 (% of theory) (mean)	94±18	40
FEV_1/FVC (% of theory) (mean)	92±13	40
Total lung capacity (% of theory) (mean)	97±15	40
DLCO (% of theory) (mean)	76±14	40
Cutaneous lesions	63 (97)	65
Angiofibroma	58 (92)	63
Laser therapy	8 (14)	58
Local mTORi	2 (3)	58
Hypomelanotic macules	39 (64)	61
Shagreen patch	16 (26)	61
Ungual fibromas	29 (48)	61
Oral disease	42 (100)	42
Pits	42 (100)	42
Pits on maxillary teeth		20
Total number of pits (mean)	24.5±22.8	20
Number of teeth with pits	5.8±1.9	20
Minimal number of pits for each maxillary tooth	0.6±1.2	20
Maximal number of pits for each maxillary tooth	7.2±4.9	20
Pits on mandibular teeth		20
Total number of pits (mean)	15.4±9.1	20
Number of teeth with pits	5.3±2.4	20
Minimal number of pits for each mandibular tooth	0.3±0.7	20
Maximal number of pits for each mandibular tooth	5.1±3.1	20
Intraoral fibromas	27 (64)	42
Sclerotic bone lesions	34 (68)	50
Ophthalmologic lesions	6 (13)	45
Hamartoma	6 (100)	6
Hypopigmental lesions	2 (33)	6
Cardiac lesions	13 (23)	56
Rhabdomyoma	5 (13)	39
Cardiac dysrhythmia	3 (8)	40
Cardiac conduction disorders	6 (15)	40

DLCO, Diffusing capacity of the Lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LAM, lymphangioleiomyomatosis; mTORi, mammalian target of rapamycin inhibitor.

For the patients, there was no correlation between the physical composite score and genetic mutation, neurological lesions, epilepsy, pulmonary disease, nephrological disease and cutaneous lesions. Nevertheless, the parameter which affected the mental composite score of quality of life was the presence of TAND (p=0.042) (online supplementary data table 3).

For the patient's family, there was a correlation between quality of life and organ damage with the role of genetic mutation (p=0.0266). On the contrary, for the psychological burden on the patient's family, there was a significant correlation with pulmonary lesions (p=0.011) and epilepsy (p=0.011) (online supplementary data table 4).

Description of patients with mTOR treatment

Eighteen patients were treated by mTOR inhibitor (mTORi) (table 3 and online supplementary data table 5). The majority of patients were treated for AML (56%) or SEGA (22%). Other patients (22%) were treated in the context of kidney transplantation or by topic mTORi form for cutaneous involvement.

Side effects were reported in 41% of patients, but only two had stopped their treatment, one for thrombopenia and one for severe depression and headache.

Evaluation of the multidisciplinary care programme for adults

The multidisciplinary evaluation in CHU de Bordeaux allowed us to obtain a follow-up of the patients and an evaluation of TSC targeting organs, according to the recommendations (table 5). Cerebral MRI was not timely performed in patients under 25 years old free from SEGA (66%). Explorations carried out for the annual monitoring were personalised, according to the previous results obtained, under the responsibility of two TSC experts.

Multidisciplinary consultation meetings were set up before any treatment decision or intervention, collegial discussion of follow-up and genetic testing or counselling (11 cases were submitted). These meetings were conducted in the presence of

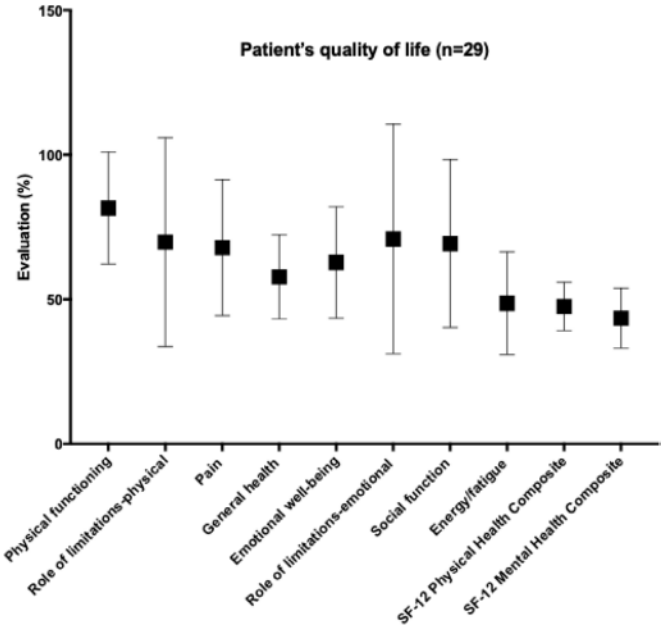

Figure 1 Evaluation of patient's quality of life with 36-Item Short Form Health Survey (SF-36) test.

Table 5 Frequency of explorations according to international recommendations

Recommendations	Monitoring rate	Value (%)	n
Patient evaluation			41
Brain			
TAND	Annual	41 (100)	41
EEG	Determined by clinical need	13 (32)	41
MRI	Every 1–3 years if under 25 years old	4 (67)	6
Kidney			
AML imagery	Every 1–3 years	40 (100)	40
Blood pressure	Annual	41 (100)	41
eGFR	Annual	41 (100)	41
Lung			
Clinical examination	Annual	41 (100)	41
Asymptomatic			
High-resolution CT	Every 5–10 years	21 (91)*	23
Pulmonary cyst			
High-resolution CT	Every 2–3 years	18 (100)	18
Pulmonary function testing	Annual	16 (89)*	18
6 min walk	Annual	17 (94)*	18
Skin			
Examination	Annual	41 (100)	41
Teeth			
Examination	Annual	39 (95)	41
Heart			
ECG	Every 3–5 years	40 (97)	41
Eye			
Ophthalmologic evaluation	Annual if ophthalmologic lesions	6 (100)	6

*When examinations were not performed this was usually due to lack of patient compliance.
AML, angiomyolipoma; EEG, electroencephalogram; eGFR, estimated glomerular filtration rate; TAND, TSC-associated neuropsychiatric disorder.

TSC experts (nephrologists, neurologists, radiologists, dentists, dermatologists, geneticists and urologists).

If necessary, a psychologist assessment was also performed: 23 of the 41 patients (56%).

Finally, we conducted a satisfaction survey. There was global patient satisfaction: organisation, expectations, rhythm of follow-up, knowledge of disease and targeting organs (online supplementary data table 6).

On an average follow-up of 588 days, there was no change in GFR, or in respiratory parameters and in neurological manifestations.

DISCUSSION

In this paper, we described a French cohort of adult patients with TSC, with an evaluation based on a multidisciplinary management model.

The 2012 International Tuberous Sclerosis Complex Consensus Conference established recommendations for the diagnosis and treatment of TSC.[10] Due to the multiorgan damage that can occur during TSC, a multidisciplinary approach in its management was recommended in 2019.[15] These recommendations were produced via a three-step process. This starts by identifying a single individual to begin organising care (step 1), then establishing a small core team (step 2) and, finally, establishing a larger MDT (step 3). Since 2015, our multidisciplinary day hospitalisation has been organised, according to these recommendations. Different manifestations of TSC may lead to complications and may evolve over a patient's lifetime. The expertise of various disciplines is then required to efficiently take care of patients with TSC.[16]

Individual care is also necessary. Clinical phenotypes of TSC may differ widely between patients, ranging from a milder form (such as a single manifestation of TSC) to more severe disease (with a combination of organs involved).[1 3 14] In addition, many manifestations of TSC have age-dependent expression and thus require regular evaluation.[18] These factors taken together complicate the evaluation and management of TSC.

To date, our cohort has had a limited number of patients with TSC. However, our TSC cohort presented a full range of organ damage from neurological lesions to dental lesions, with a description of neuropsychological disorders, in the context of global and multidisciplinary care. The main data missing from our cohort were genetic analysis. Genetic testing was not required for some of our patients, as clinical manifestations were sufficient for TSC diagnosis.[10]

Nevertheless, this management resulted in optimal evaluation and management of TSC with few constraints for patients. Only the MRI brain assessment was difficult to perform in the context of a day's hospitalisation. Patients had a large number of exams with a specific duration of exploration, in a limited time. We provided patients with prescriptions for brain MRIs to be performed externally. This approach was based on personalised monitoring specific to each patient, as promoted in the latest recommendations for patient care with TSC.

Physicians remained the main source of TSC information for patients in our cohort. We observed that many patients needed more information and knowledge about their pathology, including their organ damage and the risks linked to organ involvement.[19] This multidisciplinary approach also increased patients' compliance with follow-up and their involvement in the follow-up.

We described an adult TSC cohort. In the literature, TSC cohorts are mostly paediatric. Our patients were older at

diagnosis than in other cohorts, with age at diagnosis of 1 (0–69) year in the Tuberous Sclerosis Registry to Increase Disease Awareness study.[20] This difference is probably due to less severe involvement, and is probably linked to more mosaicism or intronic mutation (potentially explaining the large number of patients found without mutation in our cohort).[21–23] However, our cohort had similarities with other cohorts in terms of gender balance and predominance of the TSC2 mutation.[20]

We also had a lower proportion of epilepsy than other cohorts, which may explain the later diagnosis of TSC in our patients.[20 24 25] Nevertheless, we observed a higher proportion of brain MRI abnormalities. Due to the adult age of the patients and recruitment via the nephrology department, we observed a large proportion of AML compared with the other cohorts.[26 27]

Although the proportion with a history of rhabdomyomas was low,[20] we detected a relatively high frequency of conduction disturbance and arrhythmia, sequelae of cardiac rhabdomyomas.[28]

Our cohort had the particularity of including patients' quality of life at the physical and psychological levels. The main cohorts that consider quality of life include children and not adults.[29 30] Our results in terms of quality of life are similar for physical and mental composite scores to those found in populations of haemodialysis patients.[31] The second particularity is that we are also interested in the quality of life of the family of adult patients, which can be affected just as much as that of the patients. Therefore, from our point of view, psychological assessment and follow-up are crucial for family members.

In conclusion, we obtained an accurate description of a cohort of adult patients with TSC. Our model of a multidisciplinary approach enabled us to deliver optimal management of patients with TSC with a high level of patient satisfaction.

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Contributors PP planned the study, conducted a survey and drafted and revised the paper. JA conducted the global survey in day's hospitalisation. EJ and NG conducted the radiological survey. LI conducted the psychological survey. MPR performed statistics. MF and RD conducted the dental survey. CC conducted the nephrological survey. CR planned the study and drafted and revised the paper. All authors approved the final version of the manuscript.

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