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► To cite this version:

Claire Bar, Rouba Ghobeira, Rita Azzi, Dorothée Ville, Audrey Riquet, et al.. Experience of follow-up, quality of life, and transition from pediatric to adult healthcare of patients with tuberous sclerosis complex. *Epilepsy & Behavior*, 2019, 96, pp.23 - 27. 10.1016/j.yebeh.2019.04.027 . hal-03486416

HAL Id: hal-03486416

<https://hal.science/hal-03486416>

Submitted on 20 Dec 2021

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**Experience of follow-up, quality of life and transition from pediatric to adult health care
of patients with Tuberous Sclerosis Complex**

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Declarations of interest: none

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Introduction

Tuberous sclerosis complex (TSC) is a multisystemic genetic disease with high clinical variability and age-related manifestations. These characteristics add to the complexity of transition to adulthood. This study aimed to explore the perception of medical follow-up and transition experience in a large group of patients with TSC who presented epilepsy in childhood.

Method

This multicenter French study included TSC patients aged 18 years or older who developed epilepsy before the age of 16 years. A questionnaire specifically designed for the study explored patients' opinion through 270 questions covering different aspects of their social, familial, professional and medical course.

Results

The questionnaire was sent to 72 patients and 60 patients were included in the study (83% response rate) with a mean age of 32 years (18-55 years). Cognitive impairment was present in 80% of patients and half of questionnaires was completed by the family. Pediatric care was coordinated by the child neurologist and was more regular and multidisciplinary than adult care. Epilepsy had the best follow-up followed by renal issues. Unmet needs were identified for psychiatric and behavioral disorders, both in children and adults. Respondents considered the help in achieving autonomy better in adult care. Only 50% of patients with a normal intellectual development had clear knowledge about their disease and the need for a regular monitoring. Two-third of respondents estimated that they had a transition experience between 16.5 and 21-year-old, considered as good in 60% of them. Seventy percent felt continuity between pediatric and adult care and only 3% of respondents felt their care would have been better if they were still followed in pediatric health-care system. The change of care structure and/or caregivers was the most stressful factor during transition and transfer.

Conclusion

This study highlights persistent issues in the regularity and coordination of TSC patients' follow-up despite established international guidelines. Although most patients had a positive transition experience, there is still an urgent need to optimize transition programs. This would be essential to maintain care continuity between pediatric and adult health systems, especially for TSC patients with epilepsy and high rate of cognitive and psychiatric impairments.

Keywords

Tuberous sclerosis complex; epilepsy; transition; transfer; quality of life; survey

1. Introduction*

The concept of transition refers to a planned process initiated in childhood to prepare children with chronic illness and their families for adult healthcare system [1]. In contrast, the transfer names the formal event of passing care from pediatric to adult healthcare providers. This period is known to be associated with a deterioration in health status of adolescent with chronic diseases [2–4]. The need for the development of effective and efficient transition programs is now well-recognized aiming to prevent negative long-term consequences on morbidity and mortality in adulthood [5,6]. Particularly, two main factors have been identified to impact the transition: The presence of intellectual disability and the progressive or « evolving » aspect of the chronic disease [7,8]. Tuberous Sclerosis Complex (TSC) represents a typical disease model where these two factors are prominent. TSC is an autosomal dominant multisystem disorder characterized by benign tumors growths in different organs [9]. The diagnosis is based on clinical criteria or the presence of a pathogenic variant in either *TSC1* or *TSC2*, two tumor suppressor genes [9]. Although most organs can be affected during lifetime, the phenotype severity is widely variable between individuals and the spectrum of clinical manifestations and their impact are age-related [10]. Epilepsy is the most common neurological symptom in TSC, affecting around 80% of patients with a seizure onset before 3 years of age in more than 80% of them [11]. Seizures are partly related to the presence of cortical tubers, a hallmark of TSC consisting in focal malformations of cortical development [12]. Brain involvement also includes subependymal giant cell astrocytoma (SEGA), associated with a risk of obstructive hydrocephalus that decreases after the age of 25 years [13]. Kidneys (angiomyolipoma) and lungs involvement (lymphangioleiomyomatosis,

*Abbreviations:

SEGA, subependymal giant cell astrocytoma, TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex.

usually seen in women) often become major medical issues later during adolescence and adulthood [10]. Moreover, TSC is associated with a range of neuropsychiatric manifestations termed tuberous-sclerosis-associated neuropsychiatric disorders (TAND) [14]. Almost 50% of TSC patients have some degree of intellectual disability, autism spectrum disorder or attention deficit hyperactivity disorder [15].

Given the wide range of TSC manifestations and their age-related expression, a multidisciplinary monitoring and management is needed for all individuals, based on international recommendations [16]. A care coordination among medical specialties from childhood to adulthood is therefore mandatory, especially during the critical transition from pediatric to adult health care services [17–21]. Exploring patients' and families' point of view is the first step to gain insight difficulties related to this period and to identify interventions that might improve the process of transition and transfer in this population [7,22].

Although the literature addresses some issues and recommendations for the transition of children with epilepsy [8,17,23–26], only few studies have focused on the specific needs of TSC patients and they included a limited number of patients [20,22,27,28].

In the current study, we aimed to describe the perception of transition experience and to compare the childhood versus the adulthood care and follow-up in a large group of patients with TSC who presented epilepsy during childhood.

2. Material and Methods

2.1. Survey development

We used a questionnaire developed by a group of experts under the aegis of the Wyeth Foundation with the support of IPSOS Institute (a French institute specialized in survey management and data collection) to study the long-term outcome of various chronic pediatric diseases. This questionnaire is based on a common structure with some specific questions

1 adapted to each disease. In this study, we adapted for the TSC the questionnaire originally
2 developed for epilepsy and already used in the Dravet syndrome [24]. The final questionnaire
3 consisted of 270 close-ended or semi-open-ended questions divided into 6 parts: (1) Past
4 history and initial diagnosis, (2) General and social-professional situation, (3) Quality of life,
5 (4) Transition from pediatric to adult health care system, (5) Sexuality and fertility and (6)
6 Current medical condition. Quality of life was analyzed with the Quality Of Life Scale
7 (QOLS) that evaluates the current well-being perception [29] and the Multidimensional
8 Fatigue Inventory-20 (MFI-20) that evaluates patient fatiguability [30]. The transition part of
9 the questionnaire was divided into three sections: pediatric follow-up, transition/transfer to the
10 adult health-care system, and follow-up during the first years of adult healthcare. The medical
11 questionnaire was divided according to the different organs potentially affected in TSC: brain,
12 kidneys, heart, lung, skin, eyes, bones, teeth and liver. All the results presented in this study
13 come from this questionnaire and not from the physician's experiences.

15 2.2. Participants

16 We included patients aged 18 years or older on January 1st 2014, with a confirmed diagnosis
17 of TSC and who presented epilepsy before the age of 16 years. Patients were identified by
18 survey among clinicians from 6 pediatric and adult neurology university centers in France
19 within the network of the reference center for rare epilepsies and TSC (Necker-Enfants
20 Malades and university hospitals of Saint-Etienne, Lille and Lyon) and the French association
21 for TSC (ASTB). Participants were informed by telephone call of the study and its objectives
22 and about the need for a written consent to participate. The questionnaires were then sent by
23 mail with the written consent documents after verbal consent to participate. The study
24 protocol was approved by the ethics committee of our institution and written informed
25 consents for participation were obtained from all participants or their legal guardians.

3. Results

3.1. Demographic and genetic data

Questionnaires were sent to 72 patients and responses with consent were obtained for 60 of them (83%). Half of the questionnaires were completed by the family since the patient was not able to answer the questions on his own, however, in 10 patients, parents specified that they involved their child on as many questions as possible.

Mean age was 32 years ranging from 18 to 55 years and 49% of patients were females. TSC diagnosis was made during the first decade in most patients (85%) and before the age of one year in 36 patients (60%). Ten percent had a prenatal diagnosis. Thirty-two patients (53%) had a genetic testing with a pathogenic variant identified in *TSC2* for 68% of them and in *TSC1* for 32% of them. This pathogenic variant appeared *de novo* in 60% of patients tested.

3.2. Pediatric follow-up:

Child neurologists provided the coordination of care during pediatric follow-up. All patients had epilepsy and seizure onset occurred before 5 years in 70% of them. Seizures types were epileptic spasms or focal seizures in 98% of patients. All received antiepileptic drugs. Patients had a biannual or yearly visit depending on the control of epilepsy and on the type of therapies. In addition, 90% of patients had a multidisciplinary clinic every 2-3 year in alignment with our practice. This multidisciplinary clinic or day hospital included child neurologist visit, EEG, brain imaging, renal function tests and ultrasounds. During these clinics, other specialists, mainly the pediatric nephrologist, child psychiatrist, ophthalmologist or dermatologist, were included in the follow-up upon the patient's needs (86% of patients). Seventy percent had at least one consultation with a child psychiatrist. Around 55% had autism spectrum disorder (ASD) ASD diagnosis was based on the expert evaluation with

DSM criteria (Diagnostic and Statistical Manual of Mental Disorders) and Autism Diagnostic Interview (ADI). 45% of them having regular follow-up. Anxiety, opposition, hyperactivity, agitation and depression were detected in almost 65% of patients but only 25% had behavioral disorders' treatment as risperidone or methylphenidate and around 35% had a regular therapy program with a psychologist. A formal neuropsychological evaluation was performed in 80% of patients, with 70% having at least 3 evaluations during childhood.

3.3. Current medical condition and follow-up

Sixty-three percent achieved epilepsy remission during infancy. Fifty-four patients (90%) still had antiepileptic therapy and 62% of them reported a regular follow-up by a neurologist. The others were followed by their family physician who, in many cases, renewed the therapy prescription without any additional investigation. Twenty-five percent reported SEGA with a regular neurological follow-up in 75% of them. In these patients, the last MRI or brain scan was performed at an average of 7 years before this questionnaire (range 6 months-15 years) and only 15% continued a regular brain imaging. Cognitive impairment was present in 48 patients (80%) and psychiatric disorders in 42 patients (70%). However, only 20 % had pharmacologic therapy targeting these disorders and 13% had a psychological or psychiatric follow-up.

Forty-three patients (72%) presented angiomyolipoma and 78% were followed by a nephrologist but only in 40% at a regular basis (every 2 years). For the remaining 30%, a quarter of them kept on the ultrasound or MRI regular follow-up for angiomyolipoma. Lungs involvement was present in 16% of female patients, with a regular follow-up by a pneumologist in all of them. All patients had skin manifestations with a dermatologic follow-up in only 35% of them.

3.4. Current living and socio-economic conditions:

Current living situation was available for 54 patients (90%). Twenty-nine patients (54%) lived with their family, 16 patients (30%) lived alone independently and 9 patients (16%) lived with a partner. Fifty-two percent required special education programs. A university education degree was achieved for 9/60 patients (15%) while 45% of parents had one. A stable professional life was reported by 18/48 respondents (37%) but 65% of them declared a salary below the minimum income threshold in France.

3.5. Impact of TSC and quality of life

Seventy-five percent of respondents thought the disease to be a cause of isolation and social withdrawal and for 66% an object of discrimination. TSC negatively impacted the family life of 75% of respondents as well as their personality and relationships (78%). One third of respondents (34%) evaluated the quality of life as mediocre, 18% as bad, 38% as fair, 7% as good and 3% as excellent. Sixty percent reported frequent sadness with 38% of high anxiety and 60% of depressed feeling. Forty percent of respondents reported having no social or sportive activities, without a medical reason for 85% of them. Only 15% of respondents were optimistic about the state of health for the five next years.

3.6. Transition experience

Two-third of respondents experienced transition. The transfer of patients from pediatric to adult health care occurred between 16.5 and 21 years. The transition process begun mainly 1 to 2 years before transfer. Seventy five percent of respondents felt continuity between pediatric and adult care. However, one third estimated not to have experienced a transition process. Among respondents who experienced transition, 60% of them considered it as good. They felt accompanied during this transition period and had clear indications on the adults'

care pathway, the name of the adult referral physician and the name of the care institution if it changed, as for pediatric centers with no adult clinics. The group of respondents who considered their transition as good stated that adult physicians had clear knowledge about their medical history and that they obtained detailed information about their diseases compared to a more scattered knowledge and information in the group with a bad transition experience. New places (non-pediatric hospitals) and new faces (adult care providers) were the most difficult factors to face, increasing the stress during the transition. Among patients without cognitive impairment, only 40% reported having knowledge about their pathology, being able to explain their disease in few sentences, and 50% about the necessity of a regular follow-up. However, patients and families agreed on the need of transfer in adult care. Although they felt that the follow-up was not very regular, only 3% of respondents thought they would have been better followed if they had stayed in the pediatric health-care system. We investigated also the relation between patients and physicians during pediatric and adult follow-up. Dedicated time and coordination of care were better perceived in pediatric age compared to adult care but the help in feeling autonomous was better in the adult care (table 1).

4. Discussion

This study aimed to explore the socio-professional and medical follow-up along with the transition experience in a large group of adult patients with TSC who presented an epilepsy during childhood. The use of information arising directly from patients or their parents allow a global and deep understanding of their point of view regarding their concerns and experiences of the medical health care system. The high responders' rate (80%) in our study reflects the interest of patients and their families for such surveys and their availability to provide their point of view.

1 The prevalence of TSC manifestations in this study was congruent with the data of the
2 literature [12]. Epilepsy is well known to be associated with intellectual disability [31,32], as
3 shown by the high proportion of cognitive impairment reported in our population (80%). The
4 diagnosis of TSC was made during the first decade in most patients so that these patients had
5 a long follow-up in the pediatric health-care system. During this period, most patients
6 benefited of a regular and multidisciplinary care that involves different specialists of TSC
7 manifestations, usually coordinated by the child neurologist. This follow-up was established
8 following the international guidelines [16] and is part of the objectives of the French reference
9 centre for rare epilepsies.

10 In adult care, almost 40% of patients did not have a regular follow-up by a neurologist. This
11 might be explained by the epilepsy remission in 63% of them even though 90% still had
12 antiepileptic therapy. Although we did not explore the quality of the follow-up by the general
13 practitioner or the institution physicians, some patients reported that it was often limited to the
14 renewal of the prescriptions delivered 10 years before or more. The follow-up of SEGA was
15 another major issue as there are reported cases of SEGA enlargement during early adulthood.
16 Many patients of our cohort had their last MRI before adolescence as the last imaging was
17 performed at an average of 7 years before this survey. A higher attention should be given to
18 renal angiomyolipoma follow-up, the first cause of morbidity and mortality in adults with
19 TSC [33], as only 40% of patients with known angiomyolipoma in this group had a regular
20 imaging follow-up. Pulmonary involvement might be underestimated because of the young
21 age of this cohort. Skin manifestations were present in all patients but followed by a
22 dermatologist in a third (35%). Despite the known psychological and cosmetic impact of
23 angiofibroma in adolescents and early adulthood [22,27,28], this lack of follow-up might be
24 explained at least partially by the onset or worsening of renal and pulmonary life threatening
25 symptoms at this age, the lesser importance given for these dermatologic problems considered

1 as cosmetic, especially for patients in institutions, and possible negative previous experiences
2 of therapies. The new topic therapies based on m-Tor inhibitors should encourage families
3 and patients to seek again dermatology care [34–36].

4 Less than half of the patients in our study lived independently and a minority obtained a
5 university education degree and a stable professional life. The high proportion of patients
6 presenting psychiatric disorders (70%) might contribute, along with the intellectual disability,
7 to the limited autonomy achieved by these patients in their social, professional and personal
8 life [22]. Most patient suffered of social isolation (75%) and discrimination (66%) that limit
9 their ability to develop relationships, as reported by a previous smaller cohort study [22]. The
10 perception of the quality of life is thus severely affected, leading to depression symptoms
11 reported by more than half of respondents. Although most patient (70%) had several
12 neuropsychological evaluations during infancy, only a minority (13%) reported having a
13 psychological follow-up during adulthood. This cannot be due to a limited care access since,
14 in France, health care presents a free access for patients with chronic diseases. Patients,
15 families and physicians are probably less aware of the psychiatric disorders and possible
16 therapies. They are usually overwhelmed with other manifestations of TSC that are life
17 threatening resulting in underdiagnosed and undertreated major quality of life issues [13]. A
18 TSC-associated neuropsychiatric disorders (TAND) checklist has been recently developed to
19 explore the multidimensional biopsychosocial manifestations of TSC [37]. This simple tool
20 should be used to screen for TAND at least annually and at different key developmental time
21 points in order to explore the different developmental domains [13]. This was not possible at
22 the time of this study as the TAND was not yet translated in French neither validated. As
23 mental health issues may become more prominent during adolescence or adulthood, early
24 recognition of these neuropsychiatric disorders should allow early intervention programs
25 targeting the needs of these children [8,18,22].

1 As already reported for the management of TSC patient in the German healthcare system,
2 follow-up in adulthood appears less regular and structured compared to pediatric follow-up
3 [28]. The pediatric approach is inherently multidisciplinary as pediatric neurologists often
4 face developmental diseases requiring multidisciplinary care. Parents are also more involved
5 during this period, actively participating to the coordination of care with the pediatricians.
6 This organization of pediatric care and the important place of the family during this period is
7 however associated with an insufficient development of patient's autonomy, as reported by
8 80% of respondents in this study. Previous reports highlighted the lack of patients' knowledge
9 regarding TSC manifestations and their consequences [21,22], as in 60% of patients of our
10 study who had the intellectual ability to understand this. Therefore, the process of transition
11 and transfer to adult health care services is particularly challenging. It should emphasize the
12 knowledge of the adolescent and young adult of his disease symptoms and optimal follow-up.
13 This awareness increase is mandatory as the families become less present and the adult
14 healthcare system might be less aware and familiar with TSC [18,22].

15 Although the need of a continuum of care from pediatric to adult health services in patients
16 with chronic conditions is widely recognized in the literature, this point has been recently
17 addressed for patients with childhood-onset epilepsy [17,23,24,26,28,38–40]. Previous studies
18 using patients- or parents-driven information to explore different aspects of TSC impact have
19 provide evidence of the significant burden of the disease for the patient and his family
20 [22,27,41–44]. Mental health disorders are frequent in this population and may become more
21 prominent during adulthood, with an impact on all the aspect of the daily life and medical care
22 of these patients [8,18,22].

23 Most respondents (75%) felt continuity between pediatric and adult care system and two-third
24 had a transition experience, estimated as good in 60% of them. One third estimated not to
25 have experienced a transition process. This is to emphasize as these results were obtained due

1 to a networking of the medical teams involved in the reference centre and without any defined
2 program at the date of this questionnaire. Forty percent considered that the transition was not
3 optimal, emphasizing the need to develop a well-identified and planned program of transition.
4 The age of transfer in our study was between 16.5 to 21 years, concordant with the American
5 recommendations for chronic diseases [45]. However, the latter recommends starting
6 transition planning at 12 years while it begun much more later for our patients [45]. Early
7 initiation of transition process might facilitate the identification of risk factors for
8 unsuccessful transition such as unstable family environment and should enable youth to
9 acquire autonomy in their care management [8,45]. In our study, the pediatric follow-up was
10 transferred to an adult neurologist or a general practitioner and not as part of a
11 multidisciplinary STB follow-up as during pediatric care. Given the multisystemic
12 involvement of TSC, one of the solutions proposed to optimize the transition of these patients
13 would be a multidisciplinary follow-up in a structure dedicated to TSC patients throughout
14 their lifetime [17,18,20]. These clinics would decrease the stress reported by respondents
15 related to the change of care structure and care providers. The development of these clinics
16 seems unlikely in most country, this study shows however the need to improve the
17 multidisciplinary follow-up of these patients, especially for the detection and management of
18 the associated psychiatric disorders. The optimization of this follow-up requires close
19 collaboration between pediatric and adult care providers to develop transition programs
20 adapted to each healthcare system [20]. In this perspective, Peron et al. provided a list of basic
21 tips to be considered by healthcare professionals while establishing a transition process for
22 TSC patients [20]. TSC patients' associations also have a central role in this relation between
23 patients, families and care providers through the diffusion of information on the health care
24 pathway in TSC [20].

1 Some limitations must be considered in our study. Our data relates to a specific population of
2 patients with TSC who developed epilepsy during childhood and who thus presented a high
3 rate of cognitive impairment. This population might be the most severe in the spectrum of
4 TSC. Consequently, half of our questionnaires were completed by parents instead of the
5 patient himself. The answers may thus reflect the caregivers' point of view more than the
6 actual needs of the patients, especially regarding to the impact of TSC on quality of life.
7 However, parents point-of view is important for these patients as they are the main
8 interlocutors with the physician and they have special needs and concerns [22]. During
9 childhood, most patients of this cohort were followed in specialized centers for rare epilepsies
10 that might have emphasized positive and organized aspects not representative outside this
11 network. The adult follow-up was more widespread with no "uniform" care pathway resulting
12 in care gaps.

14 **5. Conclusion**

15 This study explored follow-up and transition experience of a French group of patients with
16 TSC who developed epilepsy during childhood. Despite international guidelines for the
17 management and follow-up of TSC-related manifestations, this study emphasizes the need for
18 a better regular and coordinated surveillance of patients with TSC, especially during
19 adulthood and mainly for psychiatric disorders. Even though most respondents experienced a
20 good transition process, one third did not experience a transition at all. Increasing awareness
21 of physicians on TSC symptoms and age long follow-up should improve care programs
22 during transition and transfer. Work on implementation of patients' education programs and
23 patients' empowerment using specific tools as TAND is essential to "bridge the gap" between
24 pediatric and adult health care systems and improve the long-term quality of life of patients
25 with TSC.

1

2 **Acknowledgements:**

3 We are thankful for the patients and families for their participation, for the ASTB, the French
4 association for TSC in France for their support, for Mrs Caroline Wenzel for her technical
5 support and follow-up of the questionnaires.

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Table 1

Patient or parents' perception of the relationship with the doctor during pediatric and adult follow-up (% of "yes" answer to the question).

	Pediatric care	Adult care
Did your doctor help you?	80%	60%
Did your doctor gave you enough time?	70%	45%
Did your doctor help you to feel well?	56%	45%
Did your doctor help you to feel autonomous?	20%	58%
Did your doctor coordinated care?	80%	50%