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Experience of follow-up, quality of life, and transition from pediatric to adult healthcare of patients with tuberous sclerosis complex

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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 patients with TSC 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 courses.
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 were 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-thirds 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 that their care would have been better if they were still followed in pediatric healthcare 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 the follow-up of patients with TSC 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 patients with TSC with epilepsy and high rate of cognitive and psychiatric impairments.

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, the following 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

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

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typical disease model where these two factors are prominent. Tuberous sclerosis complex is an autosomal dominant multisystem disorder characterized by benign tumor 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' involvements (lymphangioleiomyomatosis, 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 TSC-associated neuropsychiatric disorders (TAND) [14]. Almost 50% of patients with TSC have some degree of intellectual disability, autism spectrum disorder (ASD), or attention-deficit hyperactivity disorder [15].

Given the wide range of TSC manifestations and their age-related expression, a multidisciplinary monitoring and management are 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 healthcare 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 patients with TSC, 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 adapted to each disease. In this study, we adapted for the TSC, the questionnaire originally developed for epilepsy and already used in the Dravet syndrome [24]. The final questionnaire consisted of 270 close-ended or semi-open-ended questions divided into 6 following parts: (1) past history and initial diagnosis, (2) general and social-professional situation, (3) quality of life, (4) transition from pediatric to adult healthcare system, (5) sexuality and fertility, and (6) current medical condition. Quality of life was analyzed with the Quality of Life Scale (QOLS) that evaluates the current well-being perception [29] and the Multidimensional Fatigue Inventory-20 (MFI-20) that evaluates patient fatiguability [30]. The transition part of the questionnaire was divided into three following sections: pediatric follow-up, transition/transfer to the adult healthcare system, and follow-up during the first years of adult healthcare. The medical questionnaire was divided according to the following different organs potentially affected in TSC: brain, kidneys, heart, lung, skin, eyes, bones, teeth, and liver. All the results presented in this study come from this questionnaire and not from the physician's experiences.

2.2. Participants

We included patients aged 18 years or older on January 1st 2014, with a confirmed diagnosis of TSC and who presented epilepsy before the age of 16 years. Patients were identified by survey among clinicians from 6 pediatric and adult neurology university centers in France within the network of the reference center for rare epilepsies and TSC (Necker-Enfants Malades and university hospitals of Saint-Etienne, Lille and Lyon) and the French association for TSC (ASTB). Participants were informed by telephone call of the study and its objectives and about the need for a written consent to participate. The questionnaires were then sent by mail with the written consent documents after verbal consent to participate. The study protocol was approved by the ethics committee of our institution, and written informed 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. Tuberous sclerosis complex 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. Seizure 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 years in alignment with our practice. This multidisciplinary clinic or day hospital included child neurologist visit, electroencephalography (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 ASD. Autism spectrum disorder diagnosis was based on the expert evaluation with DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria and Autism Diagnostic Interview (ADI). Forty-five percent of them have 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. 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 magnetic resonance imaging (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 socioeconomic 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. Tuberous sclerosis complex 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 next five years.

3.6. Transition experience

Two-thirds of respondents experienced transition. The transfer of patients from pediatric to adult healthcare occurred between 16.5 and 21 years. The transition process began 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 (nonpediatric 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 that they would have been better followed if they had stayed in the pediatric healthcare 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 socioprofessional 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 allows a global and deep understanding of their point of view regarding their concerns and experiences of the medical healthcare 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.

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

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

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 give 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 coordinate care?	80%	50%

previous experiences of therapies. The new topic therapies based on mTor inhibitors should encourage families and patients to seek again dermatology care [34–36].

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

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

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

Most respondents (75%) felt continuity between pediatric and adult care system, and two-thirds had a transition experience, estimated as good in 60% of them. One-third estimated not to have experienced a transition process. This is to emphasize as these results were obtained because of a networking of the medical teams involved in the reference center and without any defined program at the date of this questionnaire. Forty percent considered that the transition was not optimal, emphasizing the need to develop a well-identified and planned program of transition. The age of transfer in our study was between 16.5 to 21 years, concordant with the American recommendations for chronic diseases [45]. However, the latter recommends starting transition planning at 12 years while it began much more later for our patients [45]. Early initiation of transition process might facilitate the identification of risk factors for unsuccessful transition such as unstable family environment and should enable youth to acquire autonomy in their care management [8,45]. In our study, the pediatric follow-up was transferred to an adult neurologist or a general practitioner and not as part of a multidisciplinary TSC follow-up as during pediatric care. Given the multisystemic involvement of TSC, one of the solutions proposed to optimize the transition of these patients would be a multidisciplinary follow-up in a structure dedicated to patients with TSC throughout their lifetime [17,18,20]. These clinics would decrease the stress reported by respondents related to the change of care structure and care providers. The development of these clinics seems unlikely in most country; this study shows however the need to improve the multidisciplinary follow-up of these patients, especially for the detection and management of the associated psychiatric disorders. The optimization of this follow-up requires close collaboration between pediatric and adult care providers to develop transition programs adapted to each healthcare system [20]. In this perspective, Peron et al. provided a list of basic tips to be considered by healthcare professionals while establishing a transition process for patients with TSC [20]. Associations of patients with TSC also have a central role in this relation between patients, families, and care providers through the diffusion of information on the healthcare pathway in TSC [20].

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

5. Conclusion

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

Declarations of interest

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