Transition into adulthood: Tuberous sclerosis complex, Sturge-Weber syndrome, and Rasmussen encephalitis

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Summary

Children with tuberous sclerosis complex, Sturge-Weber syndrome, and Rasmussen encephalitis all have complex but differing needs in the process of transition/transfer to adult care. All three may be associated with long-term normal intelligence or a varying degree of intellectual disability. In tuberous sclerosis complex, the emphasis of care in adulthood shifts from seizure control and developmental issues to renal and psychiatric disease and other issues. In Sturge-Weber syndrome, the emphasis shifts from seizure control and rehabilitation to management of disability and migraine. In Rasmussen encephalitis, transition may be particularly complex for those with adolescent onset. Those successfully operated on for childhood onset have a static problem and the potential to do well in life.

KEY WORDS: **Tuberous sclerosis, Sturge Weber, Rasmussen's encephalitis.**

As with other pediatric epilepsies, the transition into adulthood for individuals with tuberous sclerosis complex (TSC), Sturge-Weber syndrome (SWS), and Rasmussen encephalitis (RE) has similar and also distinct issues. This article summarizes the medical and social needs of individuals with these three disorders.

Tuberous Sclerosis Complex

TSC is a genetic disorder that affects most organ systems, most commonly the brain and the skin, and is currently thought to affect one out of 6,000 individuals worldwide.[1] TSC is diagnosed according to clinical criteria,[2] and a mutation in either the *TSC1* or *TSC2* gene can be identified in at least 85% of affected individuals. Broad phenotypic variability can result from mutations in both the *TSC1* and *TSC2* genes, including within a family carrying the same mutation. Gender plays a role in TSC, as several manifestations, particularly pulmonary involvement and lymphangioleiomyomatosis (LAM), occur much more frequently in women with TSC.

The TSC gene products are components of the mammalian target of rapamycin (mTOR) signaling pathway.[1] Identification of this led to preclinical and clinical trials

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Key Points

- In tuberous sclerosis complex, care issues tend to evolve from seizure control and development in childhood to renal and psychiatric disease in adulthood.
- In Sturge-Weber syndrome, care issues tend evolve from seizure control and rehabilitation to management of disability and migraine in adulthood.
- In Rasmussen encephalitis, adolescent onset is particularly complex. Those with childhood onset who successfully underwent hemispherotomy may have better potential to be successful in adult life.
- The process of transition/transfer should ensure that these evolving concerns are addressed.

with mTOR inhibitors in the treatment of symptoms associated with TSC, including renal angiomyolipoma (AML), subependymal malignant cell astrocytoma (SEGA), and LAM. One of these compounds, everolimus, has been approved by the U.S. Food and Drug Administration (FDA) to treat TSC-related AML and SEGA.

Brain involvement occurs in approximately 95% of individuals with TSC, and symptoms can affect an individual throughout their lifetime. Ninety percent of individuals with TSC have epilepsy at some time during their life; for 70%, onset is in the first year of life. One third of children with TSC develop infantile spasms (IS), and two thirds of individuals with TSC develop medically refractory epilepsy. The onset of epilepsy during adolescence and adulthood is uncommon, but may occur. It is important to note that many individuals with TSC experience remission of their epilepsy, and are often able to taper off medications.[3]

Half of individuals with TSC have some degree of intellectual disability (ID), which may be severe; 50% have normal cognition. Autism spectrum disorders (ASDs) occur in approximately 40% of individuals with TSC. A history of IS and refractory epilepsy, as well as a mutation in the *TSC2* gene, are risk factors for both ID and ASD in TSC. Mental health issues occur in 66% of individuals with TSC, and are seen in both children and adults. Anxiety and obsessive–compulsive tendencies are common, and can be can cause considerable impairment for the individual.

TSC is a multisystem disorder, and age plays a role in the various organ involvement.[3] For example, cardiac rhabdomyoma is seen during infancy and early childhood and typically regresses; SEGA develops during childhood and adolescence and for unknown reasons loses the propensity to develop in early adulthood; renal AML, although occasionally the cause of morbidity in childhood, becomes a more significant issue during adulthood; and pulmonary lymphangioleiomyomatosis (LAM), which is thought to develop sometime post puberty.

Therefore, as individuals with TSC transition from childhood and adolescence into adulthood, many medical issues and concerns change, not only neurologic symptoms, but also many other aspects of the disorder.

As that transition occurs, the "medical team" caring for the individual also changes, and this poses similar issues and concerns as for many of the epilepsy-related disorders discussed in this supplement. The "adult medicine world" may be less aware and familiar with TSC. For families of individuals with IDs, the "adult medicine world" can also be perceived as less family oriented than their pediatric care teams. For most patients with TSC and IDs, independent living is not possible and they require varying degrees of support. Many are unable to advocate for themselves.

As an individual with TSC transitions into adulthood, many of the medical issues change. Although seizures and IDs may persist, renal and/or pulmonary issues may become more important, and may pose risks of significant morbidity and occasionally mortality. Dermatologic concerns usually persist and may become more important due to facial angiofibroma and periungal fibroma. The psychological and behavioral concerns, although often present in childhood, may appear, persist, or become more significant during adulthood.

During childhood, the major focus of attention and concern usually relates to the neurologic symptoms of TSC, particularly on epilepsy—identifying, treating, and controlling the often medically refractory seizures. The child's development should be a focus—including language and motor development and school performance. Other features of potential concern include cardiac rhabdomyoma, renal involvement, and skin features.

However, as the individual transitions to adulthood, the focus shifts. Mental health issues have a huge impact on the ability of many adults to function, and often are undiagnosed and untreated. Kidney and lung involvement often become major medical concerns, and are probably the main cause of TSC-related morbidity and mortality in adults.

The published literature does not critically address the benefits of comprehensive clinics for TSC, which admittedly may be expensive. However, it seems intuitively correct that to provide optimal medical care to individuals with TSC throughout their lifetime, TSC needs to be recognized as a complex disorder that affects the brain and also most organs and organ systems. As individuals with TSC transition into adulthood, ideally their care could transition to multidisciplinary specialty clinics designed to provide comprehensive care to adults with TSC. However, operating and maintaining these programs is expensive in costs and resources. It is unlikely that these services would be widely available to adults with TSC.

Care for individuals with TSC during the transition to adulthood would be improved by increased awareness of possible manifestations of TSC during the lifespan. This would particularly include those manifestations with possible significant morbidity, such as renal, lung, and mental health issues. Therefore, for adults with TSC, the "target

audience" for increased awareness includes neurologists as well as nephrologists, urologists, pulmonologists, and psychiatrists.

Many adults with TSC will not be able to be completely independent due to their intellectual disabilities or mental health issues. Therefore, it would also be ideal to have clinics that are able to follow individuals throughout the lifespan. Alternatively, "transition programs" could help the individual with TSC move from pediatric care to adult-oriented care. For this population of individuals with TSC, adult care providers need knowledge of the potential medical issues of TSC as well as principles of care for individuals with ID. Furthermore, support is needed for the family and care providers to help navigate many life changes, including the process of obtaining guardianship, setting up trust funds, and investigating residential living options. The family also changes with time, as parents of the individual with TSC and ID become fatigued by providing intense care to their child over the years, and their own medical issues often become more significant. And a major source of stress for the family, particularly the parents of the individual with TSC and ID, is what will happen if their child "outlives" them.

Ideally, care regarding the mental health issues will become proactive with behavioral and mental health screens as part of clinical care for both children and adults with TSC. Recognizing these issues is important, as they impact not only an individual's daily life function, but also have a significant effect on aspects of their medical care.

Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS) is a neurocutaneous disorder characterized by facial port-wine stain, leptomeningeal angioma, intracranial calcifications, and glaucoma. Neurologic signs and symptoms include seizures, mental retardation, focal neurologic signs (e.g., hemiparesis, hemianopsia), and headaches. The pathophysiology of SWS is poorly understood. The anomalous venous plexus over the cerebral surface likely impairs cortical drainage and causes venous stasis and cortical dysfunction. The etiology appears to be a somatic mutation in *GNAQ*.[4]

Transitioning SWS into adult clinics and integrating them into society has been little discussed in the literature, but it is important to consider, since most patients with SWS live well into adulthood. In one study of 55 SWS patients,[5] epilepsy, hemiparesis, mental retardation and ocular problems were the most frequent and severe features. The major impediments toward a successful integration into adult society (i.e., gainful employment, quality of life) were limited intelligence, poor social skills, poor aesthetic appearance due to the facial angioma, and poor seizure control. Although cerebral lesions followed a progressive course during early childhood, a plateau was eventually reached and the patient was stabilized. Stabilization of the lesion with time in SWS is consistent with our studies that show early demise of the affected hemisphere is associated with better cognitive function because it forces reorganization in the contralateral hemisphere when developmental plasticity is at a maximum.[6]

The Sturge-Weber Foundation database contains >5,000 patients (>2,600 adults) from 92 countries and is an invaluable resource to address important questions. One such early study performed on adults (n = 52; ages 18–63 years), found that 39% were financially self-sufficient, and 55% were either married or were marriage "eligible." Ten of the 52 respondents produced 20 children. The distribution of port-wine stains included facial (98%) and extracranial (52%). Glaucoma was present in 60%, seizures in 83%, and neurologic deficit in 65%. Glaucoma could be congenital or arise later in life. In subjects with seizures, developmental delay was present in 43%, emotional and behavior problems in 85%, special education requirements in 71%, and employability in 46%. The corresponding figures for those without seizures were 0%, 58%, 0%, and 78%, respectively.[7]

Migraine is a common problem in adults with SWS. In an Internet-based questionnaire completed by 104 adults with SWS, 74 reported migraine headaches on a regular basis (median age 25 years; range 3–64 years). Of these, 16 (22%) had been treated with triptans and two subjects had experienced transient unilateral weakness. Triptans and preventative agents for migraine often improved quality of life.[8]

In conclusion, patients with SWS are often employed as adults, unless epilepsy and ID remain a significant problem. In addition to improving seizure control, attention should be paid to emotional status (e.g., depression, low self-esteem), migraine management, glaucoma management, and improved education of society about the disorder so that the affected individuals can be allowed to reach their potential.

Rasmussen Encephalitis

Rasmussen encephalitis (or RE) is a rare inflammatory disease causing progressive unilateral brain damage.[9] The two cardinal symptoms are intractable seizures, often epilepsia partialis continua and recurring epileptic status, and progressive neurologic deficits that include hemiparesis, cognitive decline, hemianopsia, and aphasia. The management of a patient with RE patient is demanding: (1) the diagnosis is based on clinical and laboratory findings, requires an extensive differential diagnosis, and a longitudinal observation to assess the progressive nature of the disease; and (2) the treatment of RE includes immunomodulatory treatments in the attempt to slow down the hemispheric damage and the associated functional decline; however, in most cases only surgical exclusion of the affected hemisphere offers a high chance of seizure freedom though at the price

of irreversible neurological deficits.[10] The constellation of symptoms, the progressive course of the disease, and the lack of an effective and safe treatment severely impact the patient's and family's life well beyond the epilepsy itself.

RE, in its typical presentation, manifests in childhood, but early and late variants with different disease courses, are reported. Adolescent or early adult onset RE represents about 10% of all cases. Compared with typical RE, the late form differs by a more insidious onset and slower progression of motor and mental deficits, which partly preserves the quality of life.

There are two different scenarios when patients with RE are considered for transition to adult care: childhood onset and adolescence onset. For both, adolescence represents a critical time in which RE patients are undergoing many changes in their life that produce several personal and familial challenges. At this epoch, care should address the medical, psychosocial, and educational needs of adolescents, and prepare patients and their families to live with a chronic disability. The following observations are based on our experience (authors TG and SM) with 21 patients older than 14 (present mean age 23 years, range 14–39 years), selected among the 27 patients observed at the National Neurological Institute, Milan, Italy, and collected in the context of the LICE (Italian League Against Epilepsy) collaborative study group on RE.

Childhood-onset RE

An adolescent with childhood-onset RE in most cases has already had successful surgery. At the time of adolescence, the neurologic issues have been overcome and the quality of life is potentially good: Patients are seizure- and drug-free, often remarkably, and the hemiparesis resulting from surgery is usually stable. The main issues relate to the acceptance of the motor disability by the individual with RE, and by their peers, as well as the impact on developing relationships. This is the time in which the patient fully realizes her or his infirmity, and the disparity from peers. Almost invariably the patient's self-confidence decreases and depressive symptoms appear in the form of social withdrawal, self-marginalization, anxiety disorders, or frank aggressive behavior against parents and doctors who made the decision to perform the hemispherotomy. Care should focus on these psychological issues: The patient needs to be supported by the family, and the family often also needs support. The treating physician should optimize awareness (for the patient and the family) of the history of the disease and of the unavoidability of the therapeutic choice. In our experience, inclusion of individuals with RE in structured social networks (e.g., scouting, or other volunteer groups) provides a way to increase diversity and identification of peer groups, and helps them to improve self-acceptance.

A minority of RE patients have an outcome postsurgery that is nonoptimal. In this scenario, the main issues are similarly related to the hemiparesis, mental deficits, neuropsychological disabilities, and behavioral disorders—all problems that were present to some degree before the surgery but may be more profound after surgery. In addition, there are persistent seizures. At the time of adolescence, these patients may be poorly aware of the disease and have a reduced ability to comprehend their disability. The burden of the disease is mainly on the family, and there is a risk of social maladjustment. Indeed, the ID and the behavior problems, including aggressiveness, impulsivity, lack of inhibition, and iterative behaviors, may lead to social exclusion. To approach these problems, psychiatric help, that might include drug treatment, is often important. The family should be supported and the patient integrated into a trained social network, including school and employment in protected and aware environments. Finally, there is a small subset of patients with severe disabilities resulting from unsuccessful or complicated surgical treatment. In these patients who need continuous assistance, the major issues are those of any severe encephalopathy: It is important to underscore the need for social and economic help as well as for respite care for the entire family.

Adolescence-onset RE

In most cases the diagnosis is more difficult because the clinical course is less severe and more protracted. It may take months or years before the definitive diagnosis can be made. The slow progression of the disease together with the reported efficacy of immunomodulatory therapy make treatment decisions highly challenging, particularly when the dominant hemisphere is affected. The motor impairment is usually mild, and hemispherectomy is considered the last resort. The management of an RE adolescent, who, compared to a child, has a better comprehension of the disease, might focus on the issues related to the impact of the seizures and motor deficits on a person whose body (and mind) is quickly changing and who is more independent and experiencing his or her first emotional relationships. The rarity of the disease (which implies an experience of loneliness), the progression of symptoms (which implies anxiety for the future), the constellation of potentially disabling symptoms, and the uncertainty about prognosis are stressful for the patient, family, and treating physician. To address all these concerns, the physician's first step is to "budget" adequate time to understand what the patient is able/wants to know. It is mandatory to establish an "alliance" with the patient and the family, to communicate about increasing concerns, and to actively engage the patient in the treatment decision. In this process, psychological support may be needed. Finally, it is worth noting that the complexity of diagnostic and therapeutic workup requires multidisciplinary expertise and that many decisions need to be shared by the professional team.

Transition from pediatric to adult care in all the Italian RE patients did not take place. Follow-up was some-

times with the same physician who provided care for the patient during childhood. In most cases there was an agreement between physician and family (and patient) to remain under pediatric care, because of the long-lasting history of care and decisions taken together and the close "alliance" with affective linkage built over time. In most cases the patients with nonoptimal outcome and those requiring medical assistance are also still cared for by the primary pediatric neurologist. Reasons for this lack of transition/transfer were the supposed poor expertise about this rare and complex disease among most adult physicians and the reluctance of the family to leave the pediatric environment that they perceived as competent and attentive. The few families who were encouraged to move to an adult health care environment returned to the pediatric neurologic center, reporting their disappointing experience.

For an ideal transition model, we propose that the patients with good outcome, who indeed do not require a neurologist, may be followed by the original case manager or physician. In this model, the periodic medical examination would focus on an update on the quality of life with referral to an adult specialist only in the event of new problems. In contrast, youth with active problems that require medical assistance should be gradually transferred to a specialized adult care center that has the capacity to cope with the multifaceted aspects of disability. Ideally this center would have good partnerships with schools, employment counseling/training facilities, and programs to enhance leisure activities.

Disclosure

None of the authors has any conflict of interest to disclose in relation to this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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