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Outcome of childhood-onset epilepsy from adolescence to adulthood: Transition issues

R. Nabbout [a,*], D.M. Andrade [b], N. Bahi-Buisson [c], H. Cross [d], I. Desquerre [a], O. Dulac [a], T. Granata [e], E. Hirsch [f], V. Navarro [g], L. Ouss [a], P.L. Pearl [h], D. Schmidt [i], E. Thiele [j], P.R. Camfield [k], C.S. Camfield [k]

[a] Reference Centre for Rare Epilepsies, Pediatric Neurology, Necker-Enfants Malades University Hospital, APHP, University of Paris Descartes, Inserm U1129, Paris, France
[b] Department of Medicine, University of Toronto Adult Epilepsy Genetics Program, University of Toronto, Toronto Western Hospital, Toronto, Canada
[c] Embryology and Genetics of Congenital Malformations & Pediatric Neurology, Necker Enfants Malades University Hospital, Paris France
[d] UCL Institute of Child Health, London, UK
[e] Department of Pediatric Neuroscience, Foundation I.R.C.C.S. Neurological Institute C. Besta, Milan, Italy
[f] Service de Neurologie, Hôpital de Hautepierre, Strasbourg, France
[g] GH Pitie-Salpêtrière-Charles Foix, Epilepsy Unit and Department of Clinical Neurophysiology, Institut du Cerveau et de la Moelle, Paris, France
[h] Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
[i] Epilepsy Research Group, Free University of Berlin, Berlin, Germany
[j] Director, Pediatric Epilepsy Program and Herscot Center for TSC, Massachusetts General Hospital, Boston, MA, United States
[k] Dalhousie University, IWK Health Centre, Halifax, Nova Scotia, Canada

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ABSTRACT

This is the second of three papers that summarize the second symposium on Transition in Epilepsies held in Paris in June 2016. This paper addresses the outcome for some particularly challenging childhood-onset epileptic disorders with the goal of recommending the best approach to transition. We have grouped these disorders in five categories with a few examples for each. The first group includes disorders presenting in childhood that may have late- or adult-onset epilepsy (metabolic and mitochondrial disorders). The second group includes disorders with changing problems in adulthood (tuberous sclerosis complex, Rett syndrome, Dravet syndrome, and autism). A third group includes epilepsies that change with age (Childhood Absence Epilepsy, Juvenile Myoclonic Epilepsy, West Syndrome, and Lennox-Gastaut syndrome). A fourth group consists of epilepsies that vary in symptoms and severity depending on the age of onset (autoimmune encephalitis, Rasmussen's syndrome). A fifth group has epilepsy from structural causes that are less likely to evolve in adulthood. Finally we have included a discussion about the risk of later adulthood cerebrovascular disease and dementia following childhood-onset epilepsy. A detailed knowledge of each of these disorders should assist the process of transition to be certain that attention is paid to the most important age-related symptoms and concerns.

1. Introduction

This is the second paper of three that summarizes the second symposium on transition in epilepsies held in Paris in June 2016. The first paper deals with basic changes that occur in the brain and endocrine systems, bones, and psychiatric and sociological function around the time of transition both in "normal" adolescents and adolescents with epilepsy [1]. The current paper addresses some of the adult outcomes of childhood epilepsy. The third paper addresses treatment through the transition years [2]. Seizures resolve in about 60–70% of children with epilepsy as they mature into adulthood but despite seizure remission, important co-morbidities may persist. In 30–40%, seizures and co-morbidities persist into adulthood. Information about the long-term outcome for various childhood-onset epilepsy syndromes was presented in a journal supplement that summarized the first transition meeting in Paris in 2013 [3]. In the current paper, we summarize the outcomes for some particularly challenging childhood-onset epileptic disorders with the goal of recommending the best approach to transition. For clarity, we have divided these disorders in five groups with a few examples for each.

2. Disorders that may have late-onset epilepsy

2.1. Metabolic disorders

The field of metabolic systemic and brain diseases has expanded rapidly in the past 20 years. Metabolic disorders are currently more accurately diagnosed and treated in childhood with a greater number of

* Corresponding author.
E-mail address: rimanabbout@yahoo.com (R. Nabbout).

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patients surviving into adult life. Adults with metabolic epilepsy form perhaps the most difficult cohort to successfully transition from pediatric to adult medical care. Some inborn errors of metabolism only have the onset of epilepsy in adulthood and it is also not unusual to have latency periods after early-life seizure onset. The seizures return in adolescence and adulthood, sometimes with significant escalation. Clinical features in an adult epilepsy patient that may suggest an inborn error of metabolism include an atypical presentation that does not conform to a known epilepsy syndrome, a mixture of seizure types (especially myoclonia), increasing seizure severity, association with other neurologic problems plus intellectual disability, other organ disorders, a relationship between seizure frequency and eating, and unexplained status epilepticus. Table 1 lists some examples of specific metabolic disorders that may present with adult life seizures or be characterized by prominent epilepsy during adult life [4]. These may be classified as disorders of energy metabolism, lipid metabolism/storage, intoxication syndromes, and miscellaneous.

Succinic semialdehyde dehydrogenase (SSADH) deficiency is illustrative. This disorder presents with a non-progressive encephalopathy with developmental delay especially in expressive language. There is accompanying hypotonia, ataxia, and neuropsychiatric symptoms. Based on a database, there is information on 25 patients aged 18–63 years of age [5]. About 60% have persistent epilepsy with a wide mixture of seizure types but without a unifying epilepsy syndrome. Anxiety, obsessive compulsive disorder, hyperactivity, and sleep disturbance further complicate their care. In addition, there appears to be a considerable rate of SUDEP, having affected 10% of patients in the adult cohort. There is no established treatment for the underlying metabolic disorder [6].

We present two adults with other inborn metabolic errors and problematic epilepsy to illustrate the challenges to transition to adult care. A 27-year-old woman with propionic acidemia had initial symptoms of failure to thrive in early infancy. She experienced intermittent episodes of metabolic crisis with high blood ammonia. Her first seizures were at age 16 years (generalized tonic-clonic) and became more severe and catamenial at age 20. She continues with clusters of 3–4 generalized tonic-clonic seizures plus myoclonic seizures a few days/month despite trials of 9 AEDs.

An 18-year-old man with arginase deficiency was diagnosed with autism spectrum disorder at age 2 years. Seizures began at age 3 years and were controlled with topiramate. At age 17, he developed new seizure types including staring and head drops with falls and brief convulsions that have been unresponsive to 6 AEDs.

Pediatric care of both patients included experts in metabolism, neurology, genetics, and nutrition. For neither of these patients has it been possible to find adult neurological care even though they live in a major USA city with large medical centers. Problems for transition have included the rarity, severity, complexity, and multidisciplinary nature of care, unusual treatments, lack of expertise in metabolic disorders, and concerns about medical liability.

Table 1
Inborn errors of metabolism with onset or predominance of seizures during adulthood.

- Energy metabolism disorders
  - MERRF, MELAS, GAMT, GLUT1, SLC19A3 (thiamine transporter)
- Lipid metabolism/storage disorders
  - Niemann-Pick C, Gaucher 3, NCL, LIMP2, sialidosis, Lafora
- Intoxication syndromes
  - Homocystinuria, SSADH, acute intermittent porphyria, lysinuric protein intolerance, arginase deficiency
- Others
  - HI/HA

MERRF (myoclonic epilepsy with ragged red fibers); MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes); GAMT (guanidinoacetate methyltransferase); GLUT1 (glucose transporter 1); SLC 19A3 (solute carrier family 19A3); NCL (neuronal ceroid lipofuscinosis); LIMP 2 (lysine integral membrane protein 2); SSADH (succinic semialdehyde dehydrogenase); HI/HA (Hyperinsulinism/Hyperammonemia).

2.2. Mitochondrial disorders

Mitochondrial disorders are often complicated by epilepsy in children; most children with mitochondrial disorders do not survive to adulthood. However for some of the milder and later-onset mitochondrial disorders, transition to adult care will be needed. The French Network for mitochondrial diseases (CARAMMEL) has collected long-term outcome data. One study summarized the clinical course of 56 referred children with respiratory chain disorders [7]. When a DNA abnormality was identified, the etiology was a mitochondrial DNA mutation in 11, a nuclear mutation in 12, and a depletion of mitochondrial DNA in 14. In 83%, the presentation was with multisystem failure, sensory disorders or other neurological symptoms; only 17% presented with epilepsy. Over time all patients developed seizures that were "explosive" in onset in nearly 60%. Six patterns were noted: (1) Status epilepticus complicating multiorgan dysfunction (two patients) with early death; (2) Early myoclonic encephalopathy with suppression bursts (three patients); (3) West syndrome including spasms in clusters with hypsarrhythmia and psychomotor regression (eight patients); (4) Refractory status epilepticus lasting several days or weeks and ending with either death or major neurologic deterioration until a relapse several months later (21 patients); (5) Epilepsia partialis continua (EPC) on one or eventually both sides (four patients); and (6) Epilepsy in which the major seizure type was myoclonic (18 patients), consisting of either daily brief massive myoclonus, or very frequent erratic jerks involving the distal parts of the limbs and the mouth (12 patients), eventually progressing to myoclonic status epilepticus. Overall, 50% died at a mean of 9 months after seizures onset. Very few survived into adolescence.

Interventions for mitochondrial disorders have included liver transplantation [8]. One study reported the outcome for 14 patients with DGUOK deficiency, which causes a mitochondrial depletion syndrome with liver failure and variable degrees of neurological impairment with seizures developing a few years after the liver transplantation. Transplantation was during infancy in all cases and five of the fourteen survived for 7–23 years. Thus a few patients with epilepsy with onset in infancy from mitochondrial disease may survive with liver transplant and be eligible for transition to adult care. Clearly this transition will involve multiple specialities including metabolic, neurological, genetic and transplant specialists. The pharmacological interaction between AEDs and immunosuppressive treatment may be complex.

A large cohort study from Scotland identified 186 adult patients with mitochondrial disorders who had been referred to a specialty mitochondrial clinic and then followed for a further 7 years [9]. There were a wide variety of responsible DNA mutations and rates and type of epilepsy varied with the mutation. Overall, 23% had epilepsy with most having focal epilepsy ± progression to generalized tonic-clonic seizures. Focal seizures were especially prevalent in patients with m.3243A > G, which causes MELAS (mitochondrial encephalopathy with lactic acidosis and seizures). However, for patients with one particular mutation (m.8344A > G that causes myoclonic epilepsy with ragged red fibers, MERRF) nearly all had epilepsy with myoclonic seizures. Onset of seizures varied from 2 to 58 years, thus many began to have seizures during the transition years.

3. Disorders with changing problems in adulthood

3.1. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is an important cause of epilepsy that typically begins in childhood and often persists into adulthood. Tuberous sclerosis complex is a multisystem disorder affecting most organ systems and as patients age the spectrum of health concerns changes. Tuberous sclerosis complex is thought to have an incidence of 1/5500; mutations in TSC1 (hamartin) or TSC2 (tuberin) can be identified in over 85% of those diagnosed [10]. Although TSC can be inherited in an

autosomal dominant fashion, two-thirds of patients have a new mutation. Tuberin mutations are much more common than TSC1 and are associated with more severe disease. There are also sex difference in disease expression; for example, pulmonary lymphangioleiomyomatosis (LAM) occurs almost exclusively in females.

Epilepsy occurs in over 85% of patients with TSC and onset is during the first year of life in 70%. One third of infants with TSC develop infantile spasms [11]. Approximately two-thirds of patients with TSC develop medically refractory epilepsy. As patients with TSC age, epilepsy may persist and manifestations of TSC affecting other organ systems may also become significant. Renal involvement due to angiomyolioma is a major source of morbidity in adults with TSC. In women, lung involvement due to LAM may lead to a progressive decline in lung function necessitating lung transplantation. Dermatologic involvement is present during childhood although facial angiofibroma and periungal fibroma often become more prominent during adolescence and adulthood [12]. Mental health issues, particularly anxiety, occur in the majority of individuals with TSC and are often under diagnosed and undertreated [13]. Family planning and genetic counseling are important aspects of care for families of children with TSC, and for individuals with TSC as they transition to adulthood.

Due to the multisystem involvement of TSC, ideal care for people with TSC is probably a multidisciplinary clinic, either one caring for individuals throughout the lifespan or a pediatric program that transitions to an adult multidisciplinary program. Because of costs and geography, such programs unfortunately will likely not be available for all patients. However, renal, pulmonary, as well as psychiatric specialists knowledgeable about TSC should be involved. For the approximate 50% of individuals with TSC who have intellectual disability, in addition to medical concerns, transition to adulthood also involves issues such as guardianship, housing, and finances.

3.2. Rett syndrome

Rett syndrome is one of the most common causes of severe intellectual disabilities in girls, with a prevalence of 1:10,000 to 1:15,000. Greater than 90% of cases have mutations in *MECP2* (Methyl CpG Binding protein2), a transcriptional repressor gene located in Xq28 [14,15]. The evolution of symptoms in Rett Syndrome is shown in Table 2 and illustrates that problems at transition age and adulthood differ from concerns early in life. The general profile of the adult woman is slow ongoing deterioration of gross motor functioning in contrast to better preserved cognitive functioning, less autonomic and epileptic features, and overall good general health [16]. The clinical condition of Rett patients tends to stabilize over time, and their potential for prolonged survival has recently been demonstrated with survival up to age 25 years in 70–90% [17,18]. Remarkably, parental reports about their daughters quality of life are rated as "good", irrespective of age despite serious neurological, respiratory, and behavioral problems [19].

In adulthood, >50% of Rett patients are underweight with trophic skin changes suggesting a form of premature aging. Although speech is absent in most, non-verbal communication and purposeful communication may improve. By contrast, gross motor skills slowly decline over the years, with increasing musculoskeletal problems including scoliosis and osteoporosis. [16,20,21].

Epilepsy affects 30–80% with a mean age of onset of 4 years (range 0.2–27.6). A wide variety of seizure types are reported with the exception of typical absence and generalized clonic seizures. There is a general impression that seizures decrease after 10 years of age. Many symptoms and signs may easily be misdiagnosed as seizures such as laughing, pupillary dilatation, breath holding, hyperventilation, jerking, falling forward, hand stereotypies, tremor, myoclonus, and dystonic posturing. While 60–70% have good seizure control with a first or second monotherapy, episodes of status epilepticus or nonepileptic seizures persist in 80% with more than a third having drug-resistant epilepsy, which usually requires AED polytherapy [22,23].

Therefore, as young women with Rett syndrome become adults there are significant issues to be dealt with in the context of transition. Efforts would seem appropriate to attempt to maintain gross motor and communication skills. Nutrition requires careful follow-up as do concerns about aspiration pneumonia, osteoporosis, and kyphosis.

Epilepsy care should involve a regular re-evaluation of AEDs including the withdrawal of some medications in selected patients. Antiepileptic drug choice should emphasize minimizing side effects, because there is an impression that Rett patients tolerate side effects less well than others, particularly anorexia, weight loss, and osteoporosis. "Dizziness" and ataxia induced by AEDs may lead to deterioration of motor abilities and a further increase in the risk of bone fractures. Communication may persist into adulthood and is mediated by visual attentiveness, eye movements, and facial expression. This may disturbed by AED-induced drowsiness or sedation. As is the case in many intellectually disabled adults, an occasional seizure may not be "dangerous" especially if the trade off is with multiple AEDs with multiple side effects.

3.3. Dravet syndrome

Dravet Syndrome (DS), otherwise known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare epileptic encephalopathy estimated to affect 1/40,000 children [24].

Dravet Syndrome is characterized by early onset in infancy of febrile and afebrile generalized and unilateral, clonic or tonic-clonic, long lasting seizures in an otherwise normal infant. Various seizure types appear later on: atypical absences, focal seizures, brief myoclonic seizures or myoclonic non-convulsive status described as "obtundation status" (status with consciousness impairment of variable intensity) [25]. The first years are marked by long-lasting often induced by fever with frequent intensive care unit (ICU) admissions and AEDs trials.

Mutations of the neuronal voltage-gated sodium channel alpha subunit type 1 gene (SCN1A) are reported in over 75% of patients with DS [26].

Developmental delay becomes apparent within the second year of life and is followed by definite cognitive impairment and personality disorder [27,28]. Gait disturbance is frequently reported as "ataxic gait" and may evolve to a malalignment of lower limbs and genu flexum with kyphosis resulting in a crouching gait [29].

Stiripentol (STP) was approved for Dravet Syndrome in Europe and in additional countries. To date it is the only drug specifically indicated

Table 2
Evolution of Rett syndrome.

Stage 1 Pre-regression	Stage 2 Early regression	Stage 3 Pseudo stationary	Stage 4 Motor deterioration
6–18 months	1–4 years	2–10 years	>10 years
Developmental Inattentive behaviour Hypotonia Deceleration of head circumference	Rapid loss of social interaction and communication including acquired speech Stereopathies Seizures in 15% Gait dyspraxia	Severe intellectual disability Some improvement in communication Seizures in 50% and hand stereopathies Increasing rigidity Ventilatory control problems	Loss of the ability to walk Rigidity/spasticity Scoliosis Seizures

for Dravet Syndrome. Added to valproate (VPA) and clobazam (CLB), it showed efficacy in two relatively short double blind, placebo-controlled trials [30]. There was reduction in both seizure frequency and seizure duration [31]. Although seizure control is rarely complete, children seem to benefit from polytherapy with STP plus VPA and CLB or TPM (topiramate) and ZNZ (zonisamide), and the ketogenic diet. Lamotrigine may exacerbate the seizures [32].

There are several important changes as children with Dravet Syndrome become adults. Seizures tend to decrease in frequency although few patients become seizure-free; myoclonic seizures, atypical absences, and drop attacks tend to decrease or disappear in adults with DS [33–35]. Many adults will be less sensitive to fever, but can still have fever-induced seizures. A few retrospective reports highlight a change in the circadian rhythm of seizures, with seizures occurring more in sleep with age. In addition, convulsive status epilepticus leading to ICU admission is much less common in adults [32]. Polytherapy in adolescents and adults and the use of STP are issues that must be addressed by adult neurologists. (see [2] for further discussion). The family's opinion about transition may be helpful to address their needs [35].

Cognitive outcome is poor in adolescence and adulthood with most patients presenting moderate to severe intellectual disabilities [28].

Gait disturbances mimic Parkinson's disease to some degree (crouch, dystonic, small steps, en bloc turns, and antecollis) and may improve with levo-dopa [36]. However, some of these gait characteristics suggest a motor neuropathy which has been demonstrated with EMG studies and may be the result of dysfunctional sodium channels in the initial axonal segment [37].

3.4. Autism/autistic spectrum disorder (ASD)

Definitions of autism have evolved from DSM4 to DSM5 with Rett syndrome, Asperger's syndrome, and Disintegrative syndrome no longer considered separately. There is a single category of autism that swings on two criteria – deficits in social communication and restricted interests with stereotyped behavior.

Children with early-onset epilepsy are at high risk for both ASD and intellectual disability (ID), although ASD may not be recognized. When a series of 81 children with active epilepsy were screened using the DSM-IV-TR criteria, 21% were recognized to have ASD but only 8% had previously been diagnosed [38].

The link between ASD and epilepsy appears to be bidirectional. Children with ASD have a higher rate of epilepsy than the general population - 5 to 40% [39]. Intelligence quotient is an important risk factor. One study noted a prevalence of epilepsy of 21.5% in autistic subjects with ID versus 8% in autistic subjects without ID [40]. In the Connecticut study, the prevalence of autism was 13.8% in children with epilepsy and an IQ <80, compared with 2.2% in those with normal cognitive abilities [41].

Risk factors for ASD in children with epilepsy also include a symptomatic etiology [42] and onset of epilepsy in the first year of life, even when infantile spasms are excluded [43]. Children with early encephalopathic epilepsies are particularly at risk to develop later ASD with reported rates of ASD of 7%–33% in West Syndrome [44], ~24% in Dravet Syndrome [45] and 6 of 8 patients with PCDH 19 [46]. When the etiology of epilepsy is tuberous sclerosis complex, the risk of ASD has been estimated as 16–65% [47].

Other encephalopathic epilepsies such as Laudau-Kleffner Syndrome and epilepsy with continuous spike-waves during slow-wave sleep (CSWS) have been described with language and behavioral symptoms that are associated to ASD.

The outcome of ASD in children with epilepsy seems to be independent from the epilepsy outcome [48,49] although there is little information about the evolution of autism through the transition ages. The long-term outcome of ASD depends on early, intensive, and adapted interventions [50], and we presume on the capacity of adult health care teams to continue these interventions. There is little information about remission rates for epilepsy when it is accompanied by ASD.

Transition issues for people with autism and epilepsy include both treatment for epilepsy and management of autism. The epilepsy treatment does not appear to differ significantly from “routine” epilepsy care. As noted above, early intervention for autism appears to improve adult outcome especially in those with some early language and relatively normal intelligence. Improvements are often, but not always, noted in adaptive functioning, pragmatic use of language, and the severity of autism-related behavioral symptoms. There are no clear guidelines for the best management of adults with ASD. Based on the experience in pediatrics, a multidisciplinary team including social work and psychology appears to be most useful.

4. Epilepsies that change with age

4.1. Childhood Absence Epilepsy and Juvenile Myoclonic Epilepsy

The clinical course of children with Childhood Absence Epilepsy (CAE) varies and includes: 1) terminal remission ≥12 months in ~65–82%; 2) persistent refractory CAE in ~11% and 3) change in epilepsy syndrome in ~15%. Estimates of these differing courses vary considerably because most studies are retrospective with selection bias and heterogeneous populations. Few long-term population-based studies have addressed the prognosis of CAE. In four large population-based studies of childhood onset epilepsy between ages 1 month to 16 years, the proportion of epilepsy accounted for by CAE was 10–14% and in two population-based studies the proportion of Juvenile Myoclonic Epilepsy (JME) was 2–3% [51–55].

In a large case series of CAE, terminal remission occurred in 85% [51] but was somewhat lower in two population-based studies (65% and 77%) [51,56]. Remission was usually at an average of 12 years or 60 months after epilepsy onset. Persistent refractory CAE in population-based studies was noted in 2–9%, which is lower than reports from tertiary centers. Years after CAE, some patients had a change in epilepsy syndrome, primarily a change to JME. The large case series of Janz found this sequence to occur in ~4–6% [57]. A single population-based study found that 15% of children with CAE later developed JME [58]. This sequence was more likely when the age of onset of CAE was ≥9 years of age and CAE persisted after age 10 years. Significant predictors of the progression of CAE to JME were a lack of response to AEDs within the first year, absence status, EEG background slowing, and a 1st degree family history of generalized seizures. We estimate that a quarter of youth in epilepsy transition clinics have persistent CAE or JME.

Despite generally normal intelligence, the adult social outcome of children with CAE is often poor. Large case series demonstrate that up to 35% have ADD complicated by hyperactivity present at the time of diagnosis or within the first year of follow-up. Attention deficit hyperactivity disorder may be a major factor that explains why 75% of CAE patients followed into adulthood in two separate population-based studies have significant problems with schooling, occupation, routines of daily life, relations with friends, leisure time activities, housing and independence [59,60]. These adverse outcomes are independent of remission of CAE. They are not simply the generic effect of having a chronic disease.

There are no published reports of the social outcome of children with CAE who evolve to have JME, although the adult social outcome of JME itself has been studied in several large case series [61,62] and one population-based study [63]. Social problems of patients with JME in young and mid-adulthood are similar to CAE - 75% have significant adverse social complications. Behavioral and personality profiles generated by neuropsychological case series suggest that these problems are linked to frontal lobe dysfunction. Neuroimaging studies of JME also support this suggestion.

A transition clinic gives the opportunity to discuss and evaluate various issues with persistent CAE and JME patients. Topics to address include SUDEP, lifestyle issues, appropriate medications, adherence, and teratogenesis, particularly from valproate. Psychosocial issues are extremely important and include psychiatric diagnoses, education, intelligence, employment and finance, sexuality, and genetics.

4.2. Infantile spasms and Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) (the combination of tonic seizures and polyspikes with atypical absences and slow spike waves) begins at 6–8 years of age when it is not preceded by another type of epilepsy. If it is preceded by another type of epilepsy such as infantile spasms (IS), epilepsy with myoclonic-atonic seizures or infantile focal epilepsy the onset of LGS may be younger. In adolescence, tonic seizures and polyspikes often persist although atypical absences and slow spike-waves diminish and can disappear [64]. A frontal-basal ganglia loop named "secondary network" by Archer et al. [65] is involved, and since the frontal lobe is the last to mature, this could explain late onset and persistence into adolescence and adulthood. Infantile spasms (IS) involves a cortical-lenticular loop that is more posterior, involving insular and parietal areas, thus epilepsy may disappear with maturation of non-epileptic frontal lobes. The switch from West to LGS seems to result from myelination (which takes place between 6 and 18 months of age) and progressive frontal cortex maturation (from 2 years on). However, severe epilepsy may delay brain maturation, and Schropp et al. [66] reported delayed myelination in patients with persistent West syndrome. The course of IS depends on the etiology and neuropathology. Among patients with an ischemic etiology (especially perinatal), those with leukomalacia usually stop having IS whereas those with cortical atrophy following full term ischemia often continue with spasms or focal seizures. Frontal ischemia is particularly associated with focal ischemia seizures [67]. Furthermore, IS persists in most patients who had herpetic encephalitis [68]. However, switching from IS to LGS requires the presence of the corpus callosum (CC) (probably to synchronize both hemispheres) since in Aicardi syndrome (IS with agenesis of the CC in girls), IS persists without tonic seizures or slow spike waves, unless the CC agenesis is partial [69]. The switch from spasms-like to the tonic-like patterns is correlated with increased interhemispheric conduction velocity [70]. Therefore, LGS may persist because it involves frontal lobes that continue maturing into adulthood, whereas IS persists if there is cortical involvement, particularly frontal, and IS may switch to LGS with the development of myelin in the CC.

5. Epilepsies with different presentations at different ages

5.1. Autoimmune disorders

Autoimmune disorders are increasingly recognized as the cause of epilepsy in children and adults, particularly with pharmacoresistant epilepsies. Early diagnosis and treatment may avoid irreversible brain injury. There are some differences in these disorders with age that have relevance for transition. Autoimmune brain disorders with epilepsy can be broadly categorized as caused by immune reactions to intracellular antigens, which are frequently paraneoplastic, or membrane (synaptic or, neuropil) antigens, which are less likely to be related to cancer.

Limbic encephalitis is relatively uncommon in children and usually not related to cancer, while nearly all adults with this disorder have an underlying cancer. The most common antibodies are anti-HU and anti-RI [71]. Limbic encephalitis may also be related to anti-GAD 65 antibodies and is associated with systemic auto-immune disorders such as diabetes or celiac disorder [72].

Epilepsies associated with antibodies against membrane targets mainly include encephalitis related to NMDA receptor antibodies and these are typically associated with ovarian teratomas in young women [73]. Half of these patients are younger that 18 years of age and epilepsy may not be a prominent feature early in the course. In youth around the transition age, presenting symptoms are typically behavioral, cognitive, memory or speech disorders, although about 20% will have epilepsy at onset [74]. In younger children, epilepsy is more prominent and in older adults, behavioral issues are predominant.

Other epilepsy-related antibodies can target the voltage-gated potassium channel complex (VGKC), and specifically the LGI1 and CASP2 proteins. LGI1 antibodies (abs) related autoimmune encephalitis is more common in males and can affect youth of transition age [75]. VGKC abs not related to LGI1 or CASP2 abs have been reported in children. LGI1 abs disorders may primarily affect motor cortex or the hippocampus and these disorders may present as an encephalopathy with normal CSF, (i.e. no evidence of inflammation), and normal MRI [76]. LGI1-abs encephalitis may be a difficult to recognize, monophasic disorder with no detectable antibodies after a few months. In addition, because new antibody targets continue to be identified, it is prudent to store acute serum and CSF in patients of transition age who present with unexplained epilepsy and encephalopathy.

5.2. Rasmussen encephalitis

Rasmussen encephalitis (RE) is a rare disease characterized by intractable seizures, cognitive decline, and symptoms of progressive hemispheric dysfunction The disease typically begins in childhood, but a number of patients have been reported with onset of symptoms in adolescence and adulthood ("late onset" cases) [77,78]. In childhood, the mean age of onset is 6 years. After a short prodromal phase, the onset of the "acute stage" is usually stormy, with focal seizures rapidly becoming drug resistant and the appearance of epilepsia partialis continua (EPC) or status epilepticus. Brain MRI shows progressive hemispheric atrophy and cortical and subcortical signal abnormalities in the first months after seizure onset. In most cases, children develop hemiparesis and cognitive decline within one year. In this typical presentation, the formal diagnostic criteria proposed by the European Consensus Statement [79] usually allows the tentative diagnosis very close to the onset of the disease. The scales for the assessment of clinical worsening (motor scales, cognitive tests) and an adequate EEG and MRI follow-up are able to confirm the diagnosis in the following few months. Once the diagnosis is established, there is unanimous consensus that the surgical removal or disconnection of the affected hemisphere is the treatment of choice, including patients with involvement of the dominant hemisphere. In the decision-making process, seizure freedom, the expected regain of independent walking, and the potential ability of the healthy hemisphere to functionally reorganize even for language skills [80] are more important than the inevitable costs of the procedure (hemiparesis and hemianopsia, which are already present in most cases at the time of surgery).

In the last few years, at least two main problems have emerged. First the use of immunomodulatory treatment (namely steroids and intravenous immunoglobulins-IVIg) can result in delaying surgery in patients who could benefit from an early intervention. Secondly, in successfully operated patients, the post-operative inevitable motor deficits may lead to behavioral and mood disturbances once the child grows up and becomes aware of her/his disability [81].

In adolescence, the onset of RE may be more subtle. Some patients have a few seizures during childhood, the semiology of seizures may be similar to that of temporal lobe epilepsy, and EPC is less common or its appearance delayed even though unilateral movement disorders or motor deficits may be prominent. The atypical presentation and protracted course may prompt an extensive differential diagnosis and the slow worsening of symptoms may be difficult to appreciate with the common assessment scales. Once the diagnosis is reached, particularly if the motor deficits are mild and the dominant hemisphere is affected, the dilemma of best treatment is profound (immunomodulatory versus surgery). Moreover, the patient's awareness of the disease implies her/his involvement in the decision-making process and

requires sympathetic understanding of what the patient is able/wants to know and is able to fully understand.

Finally, a limited number of patients with adult-onset RE are reported up to the age of 60 years [82,83]. Two distinct patterns of disease presentation have been described: one characterized by focal motor epilepsy and the other by focal cortical myoclonus. It is generally agreed that adult-onset RE is milder than with younger onset with a mean delay between the onset of seizures and the appearance of neurologic deficits of 10 years. As in teenagers, the slow worsening of symptoms makes the diagnosis difficult, and presents challenges regarding the treatment choice. Recently a scale for the clinical assessment of adult RE patients has been proposed [84]. The results of this tool, combined with neurophysiological, neuropsychological, and imaging results may help in evaluating the progression of the disease during the diagnostic work-up, as well as the response to treatments. Hemispheric disconnection is usually not considered in adults with preserved (or mildly impaired) neurologic function and immunomodulation is usually preferred, although the benefits may be limited. In patients with severe refractory epilepsy and recurring status epilepticus that impairs the quality of life, limited cortical resection (defined by a highly congruent electroclinical picture) may be reasonably considered as the best therapeutic compromise.

In summary, managing a patient with RE requires a differentiated approach at different ages. The disease presentation and course, and the load of the cardinal symptoms (seizures, motor deficits, cognitive impairment, language disabilities, and behavioral disorder) may be different at different ages. The diagnosis of "late onset" RE may be difficult to suspect and confirm due to frequent atypical presentations and a protracted course. The tools to assess disabilities are different according to the age of onset and may not be adequate in cases with slow progression. Although the pros and cons of medical and surgical treatments vary with the age of onset, the affected hemisphere, the severity of seizures, and the associated symptoms, awareness of the disease increases with age and the role of the patient in the decision-making process becomes crucial in adolescents and adults.

6. Disorders that may not change

6.1. "Structural epilepsies"

The etiologies of the "structural epilepsies" are common throughout all age groups. However, there are some differences which may emerge over time, as well as similarities in presentation across adolescence.

First, will the clinical presentation change? Semiology can be quite variable and misleading in neonates and infants; however, with age the clinical presentation of seizures becomes similar to that of adults. As children develop more sophisticated language they can begin to convey their symptoms which may give clues to the origin of the seizures. In a longitudinal series of 120 individuals with focal cortical dysplasia, evolution of seizure semiology over time could be reviewed in 101. Sixty-three showed a change in semiology, but no new seizures appeared beyond 14 years of age [85]. Notably all but 4 patients presented with their first seizure before 20 years of age. Response to medical treatment in this group is likely to be unfavorable in the longer term – studies are clear that remission is highly unlikely. In a series of children with newly-diagnosed epilepsy in Olmsted County 1980–2009 followed for two years, nonsyndromic epilepsy accounted for 256 patients. At least one AED had failed due to lack of efficacy in 100 (39.1%) [86]. After two AEDs, seizures responded favorably to a third AED in about 25% who had epilepsy of an unknown cause whereas seizures in only 7.8% responded with structural/metabolic epilepsy. In a further series of patients with probable lesional frontal lobe epilepsy, the maximal seizure freedom rate was 25% when onset was at 13–16 years compared with 0–15% in younger patients. Individuals may show a transient period of responsiveness and in one series of patients with focal cortical dysplasia, 17% (20 patients) became seizure-free for twelve months or more; in some this lasted up to 9–12 years [85].

Many studies demonstrate that both short- and long-term seizure freedom rates after epilepsy surgery remain relatively high (40–80%), dependent on the series, extent of resection, and underlying etiology [87–90]. In one series of adults who had undergone temporal lobe resection in childhood, up to 10 years following surgery, 86% were seizure-free compared to only 35% of controls (adults who had been offered temporal lobe resection as children but who had not undergone this for a variety of reasons) [91]. In addition, co-morbidities may change after surgery. This study demonstrated a stable IQ in the initial stages postoperatively, with definitive gains seen beyond six years following surgery. This was not seen in the control group. Further, memory improvements were also seen in the operated group in functions subserved by the nonoperated side, i.e. visual memory improved in left (dominant) hemisphere resections with no change in verbal memory, whereas verbal memory improved in those who underwent right (nondominant) resection with no change in visual memory [92]. These findings contrast with longer-term studies of adults with temporal lobe epilepsy that show a steady decline in memory through adulthood [93].

There are high rates of behavior disorders in children with epilepsy [94], particularly in surgical candidates both pre- and post-surgery [95,96]. A recent study evaluated behavior outcomes after 4–11 years in a cohort of surgical and nonsurgical patients utilizing the Parent Related Child or Adult Behavior Checklist. There was no difference in any domain between the two groups but seizure-free patients, whether through surgical or medical management, had fewer symptoms in almost all behavioral domains compared to patients with continuing seizures. The most consistent predictor of improved behavior was greater behavior problems at baseline [97]. This may also be the strongest predictor of quality of life. Other studies have shown that psychopathology may have a greater impact on quality of life than seizure outcome. In the Connecticut cohort, children with epilepsy were assessed 8–9 years following diagnosis. Having "complicated" epilepsy and/or a five-year remission had few or no associations with Health Related Quality of Life (HRQoL). In multivariable analysis, psychiatric comorbidity was significantly associated with both worse child-reported and parent-reported HRQoL [98].

Finally, long-term outcomes into adulthood may include those psychosocial problems that are more likely in those with ongoing seizures; notably a great chance of unemployment, a lower rate of marriage, and having fewer children [99]. A longer term temporal lobe epilepsy study followed outcomes up to 10 years after surgery in childhood and showed significantly more educational attainments, less disability, and more independent living in those who had undergone surgery compared to the control group, although there were no differences in employment outcomes [100]. A further study of children with intractable epilepsy followed for 4–11 years to at least 18 years of age (mean age 22 years), showed all patients, both surgical and nonsurgical, were less likely to achieve an income >$10,000 than the general population but for other domains there was little difference. Seizure freedom, whether medically or surgically induced, was associated with significantly higher rates of independent living and the attainment of a driving licences.

In conclusion, in children with structural focal epilepsy who become seizure-free with or without surgery, psychopathology may change over time and quality of life may be dependent on this. Vocational outcomes are less clear- seizure freedom is related to independent living and driving, but improvements in other domains appear less secure. The emerging group of adults who have had epilepsy surgery in childhood require continuing follow-up to enable prompt evaluation of concerns should seizures recur but also with regard to emerging psychopathology.

7. Cerebro-vascular disease and dementia in adults with childhood-onset epilepsy

When children are diagnosed with epilepsy, parents want to know the long-term outcome: will the seizures will be treatable, will the

epilepsy be outgrown, and will there be an effect on learning and development? They may also want to know about adult life, social function, and health. There is some recent information raising the possibility that there is an increased risk of dementia in adulthood.

While it is well established that Alzheimer's disease (AD) increases the risk for late-onset seizures and neuronal network abnormalities [101], it is less clear if epilepsy increases the risk of adult-onset dementia. Epilepsy is a well-known risk factor for dementia in the elderly aged ≥65 years and in a multivariate analysis, epilepsy was found to be the leading risk factor for dementia in the elderly [102]. Understanding the mechanistic link between seizures and epileptiform activity and AD is a research area of growing interest. Two major candidates for this linkage are excitatory neuronal activity and the amyloid-b (Ab) peptide, which has been identified as a possible link between AD and seizures, While Ab is known to affect neuronal activity, the full-length amyloid precursor protein (APP) and other APP cleavage products may be important for the development and maintenance of cortical network hyperexcitability [101–104] and have been implicated in the development of refractory temporal lobe epilepsy [105]. Increased levels of APP mRNA and beta APP protein were found in epileptic temporal lobe and hippocampal tissue of patients with epilepsy undergoing surgery [105].

We present preliminary evidence from a well-known prospective long-term cohort of childhood-onset epilepsy [106] about possible increases in the risk of age-accelerated cognitive impairment and adult-onset dementia, and if Ab is increased in adults with childhood-onset epilepsy.

A study, presented as a poster at the meeting of the American Epilepsy Society meeting in San Diego in 2012, examined later life-cognition and brain structure in the epilepsy cohort from Turku, Finland [107]. This study now has a 50-year follow-up of children and adolescents who developed or had epilepsy in the catchment area of the hospital in Turku, Finland. Subjects and controls underwent extensive neuropsychological testing to examine episodic memory, semantic processing, language function, visuo-motor function, and executive function. The results suggested impaired cognitive function in subjects with active epilepsy and epilepsy in remission versus controls; language ($p < 0.001$), visual-motor function ($p < 0.001$), and executive function ($p = 0.003$). Of course it is possible that some of these deficits were lifelong and preceded the onset of epilepsy.

From the original Turku cohort of 245 subjects with childhood-onset epilepsy, 51 of 78 survivors with "uncomplicated epilepsy" who volunteered were assessed after 45 years of follow up by 3 T MRI, EEG, and laboratory studies [106]. Their investigations were compared with 52 of 99 matched controls who had participated in a previous study of social function in 1992.

The rate of 3 T MRI abnormalities was significantly higher in subjects than in controls (risk ratio [RR] 2.0; 1.3–3.1) specifically including findings considered markers of cerebrovascular disease (RR 2.5; 1.04–5.9) and "age related white matter changes". Even subjects with idiopathic epilepsy had higher rates of imaging abnormalities than controls (73% vs. 34%, $p = 0.002$). The presence of these imaging abnormalities suggestive of vascular disease raises the concern that children with epilepsy may be at higher risk for clinically evident stroke and cognitive changes as they age.

In addition, the amyloid-b (Ab) peptide has been identified as a possible link between AD and seizures [101]. To examine amyloid deposition in adults with childhood onset epilepsy, 43 of the "epilepsy only" patients and 46 controls were scanned with 11C–labeled Pittsburgh compound B (PIB) using Siemens HRRT. Overall there appeared to significantly more Ab in patients with epilepsy than controls. This study has not yet been published but has been presented in abstract form [108].

We conclude that long-term seizure outcomes are excellent in childhood-onset epilepsy, especially for those with "uncomplicated" epilepsy but MRI abnormalities suggestive of vascular disease may increase the risk for stroke and cognitive changes as these patients age. In addition, preliminary evidence suggests that childhood onset epilepsy is associated with increased amyloid deposition in later adulthood. It is therefore possible that the risk of adult-onset dementia is increased in people with childhood-onset epilepsy.

Table 3
Implications for transition.

- Transition is difficult to orchestrate for patients with metabolic and mitochondrial diseases complicated by epilepsy. The epilepsy may only present in adulthood as a late complication.
- Some causes of childhood epilepsy have different health concerns in adulthood. Tuberous sclerosis is a good example where childhood concerns focus around seizures and cognition while adult concerns center on kidney and lung disease and serious anxiety disorders.
- Some causes of childhood epilepsy evolve in complex patterns. Rett syndrome is particularly poignant. Surprisingly we know little about the adult outcome for autism and epilepsy, which is relatively common. Dravet syndrome shows different seizure severity in adulthood with increasing concerns about mobility.
- Some epilepsy syndromes present in childhood, may persist into adulthood or morph into other syndromes. Childhood Absence Epilepsy and its relationship to Juvenile Myoclonic Epilepsy is illustrative.
- Autoimmune encephalitis diseases vary in symptoms with age of onset and the specific antibody. Knowledge of this variation is important for planning transition and adult care.
- Children with structural etiologies for their epilepsy who become seizure-free with or without surgery may still have emerging psychopathology in adulthood that plays a major role in their quality of life.
- There is increasing concern based one cohort of children with epilepsy followed for 45–50 years that the risk of stroke and dementia is increased in adulthood.

8. Conclusion

Childhood-onset epilepsy often changes in adulthood. The seizures may increase or decrease depending on the etiology. More importantly, there are a number of other serious medical and psychiatric disorders that dominate the adult lives of some of these patients, disorders that are not as prominent during childhood.

Some childhood neurological disorders are only associated with epilepsy in adulthood even though the disorders have significant effects on the child's brain function. Some epilepsy syndromes evolve to different syndromes in adolescence and adulthood with differing treatments. Finally, some specific disorders (especially autoimmune disorders) have different clinical features depending on the age of onset even though the basic etiology is apparently the same Table 3. Without detailed knowledge of these complexities, transition to adult care is very challenging.

Conflict of interest

None of the authors have any conflicts of interest to declare.

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