Regression in Development after Seizure Onset in Tuberous Sclerosis: A Report of Two Cases

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Abstract

We report two cases diagnosed with Tuberous Sclerosis Complex (TSC) that showed relatively late onset developmental regression with loss of skills following onset of epileptic spasms at around two years of age. Both the cases were reported to be developing normally before the regression. The regression in both children was characterised by a sudden and dramatic loss of intellectual abilities, social, communication and play skills and the emergence of autistic symptoms. The loss of skills in one case temporarily improved following initial treatment with steroids, but recurred after seizures (including periods of status epilepticus) began again. In both cases, the loss of skills persisted after seizures were eventually controlled. At follow-up after 5 + years of age, one child had developed all the features of autism, whereas the child who had shown transient developmental improvement following treatment with steroids had developed a number of symptoms of autism, but not the full syndrome.

Keywords: Tuberous sclerosis; Autism; Seizure; Regression

1. Introduction

Tuberous Sclerosis Complex (TSC) is a genetic disorder with an estimated prevalence of around 1 case per 6000 to 10000 individuals (Jozwiak, 2000; Kandt, 2003). It arises from a mutation either in the TSC1 (chromosome 9q34) or TSC2 (chromosome 16p13.3) genes (Cheadle et al., 2000). The principal brain abnormalities are subependymal nodules and cortical tubers. Cortical tubers vary in number and location but most individuals with TSC have several (Shepherd et al., 1995). Cortical tubers are associated with epilepsy and focal epileptic discharges may arise from tubers or the surrounding tissue. Epidemiological studies (Harrison and Bolton, 1997) have shown that around 50-60% of individuals with TSC have intellectual disabilities and 43-86% an Autism Spectrum Disorder (ASD). ASD is an umbrella term denoting a group of related disorders that includes autism,

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atypical autism, Asperger's syndrome and 'Other' Pervasive developmental disorder. Epidemiological studies of children with autism have reported that TCS occurs on average in around 1% of cases (Harrison and Bolton, 1997). There have been reports documenting regression in development following the onset of seizures in children with TSC (Deonna et al., 1993; Humphrey et al., 2006). The regression in one of the cases reported by Deonna and colleagues occurred at 13 months of age, so it was unclear exactly how normal development was prior to the loss of skills. The regression in the other 2 reported cases occurred later in the second year and resulted in the development of autism in the case described by Humphrey and colleagues (Humphrey et al., 2006). Due to the limited number of reports, the age range during which regression occurs following seizure onset remains unclear, as does the degree to which regression follows a prior period of normal development.

The mechanisms underlying developmental regression in tuberous sclerosis have not been established. Previous retrospective research has reported associations between genetic and phenotypic manifestations and developmental outcome, which suggest potential risk pathways. Thus, several studies have reported that TSC2 mutations are associated with a more severe phenotype and a higher risk of intellectual impairments (Dabora et al., 2001; Jansen et al., 2008a). In addition, several reports have suggested that the number and distribution of cortical tubers is associated with the risk, severity and age of onset of epilepsy, as well as the risk for intellectual and behavioural abnormalities (Bolton et al., 2002; Raznahan et al., 2006). Furthermore, the type and severity of seizures appears to be associated with the likelihood of intellectual and behavioural problems (Gillberg et al., 1994; Bolton, 2004; Jansen et al., 2008b). Approximately 90% of individuals with TSC develop epilepsy and the seizures usually begin within the first year of life (Yates et al., 2011). Infantile spasms are common, but individuals frequently manifest several different types of seizures. The epilepsy is often only partially responsive to treatment. Several reports have suggested that the risk for intellectual impairments in TSC is correlated with the presence, age of onset, type (especially infantile spasms) and severity of seizures (Shepherd et al., 1995; Holmes and Stafstrom, 2007; Raznahan et al., 2007). These and other findings, when taken in conjunction with evidence from animal studies, have raised the possibility that seizures may themselves have deleterious effects on brain structural and functional development. Seizures can disrupt the normal dendritic arborisation and synaptogenesis during critical developmental periods, thereby perturbing the proper instantiation of cognitive representations within cortical networks (Holmes, 2009).

Whilst there have been a number of studies that have linked genetic risk factors to brain anatomical changes (Dabora et al., 2001) and several that have linked brain changes to epilepsy, intellectual / cognitive and behavioural deficits (Shepherd et al., 1995; Bolton and Griffiths, 1997; Goodman et al., 1997; Harrison et al., 1999; Curatolo et al., 2002; O'Callaghan et al., 2004; Raznahan et al., 2007), as well as features of epilepsy to cognitive and behavioural outcome (Jambaque et al., 1991; Shepherd and Stephenson, 1992; Jozwiak et al., 1998; Jambaque et al., 2000; Bolton et al., 2002), there have been very few studies that have examined the way the combination of all the risk factors act together to lead to cognitive, intellectual and behavioural impairments.

Here, we describe two female cases of TSC, who showed regression in their development at a relatively late age following seizure onset after an apparent period of normal development. We discuss their pattern of regression and correlate that with the current understanding of regression
and neuro-epileptic determinants of ASD in TSC. The cases are noteworthy because of the clear-cut association in time between the onset of seizures and developmental regression following a period of normal development. The aim of this paper is to add to the existing case reports of regression in children with TSC and to study the factors that contributed to the regression.

The 2 cases described in this report are part of an ongoing cohort study of cases with TSC (Yates et al., 2011). West Midlands National Health Service (NHS) multicentre research ethics committee gave the ethics approval for this study in 2001 and the approval was renewed in 2005, 2009 and 2012.

## 2. Case Vignette 1

### 2.1 Early Development

The child, hereafter referred to as CS, was born by emergency caesarean section following a difficult pregnancy. Her mother was sick throughout the pregnancy and had intermittent unexplained vaginal bleeding until 7 months gestation. Her mother also developed gestational diabetes at 7 months, which spontaneously remitted after the delivery. The gestational diabetes was poorly controlled on insulin, so labour was induced one week prior to the due date. CS was delivered by emergency caesarean section after a prolonged labour. There were no concerns regarding CS at the time of birth and there was no need for resuscitation or special care. Her early development was within normal limits. She was sitting unsupported at 5 months and walking independently at 10 months. She spoke her first meaningful words at 15 months and started connecting words into simple phrases by 19 months. She had a good vocabulary, good imaginative play and had just started toilet training when she presented with seizures at 22 months of age.

### 2.2 Seizure Presentation

Her seizures probably first began with episodes of transient loss of consciousness, characterized by staring episodes, which were happening more than once daily. They were soon followed by episodes of epileptic spasms. These initially started with deviations of both eyes to the left side, followed by deviation of the neck to the same side and flexion of both arms and wrists. Within a few weeks, these spasms also started involving flexion of the lower limbs, which meant that the whole body folded up during the spasms. Average duration of a spasm was 6-10 seconds and the maximum duration recorded was 20 seconds. The spasms occurred in clusters averaging 30 minutes each throughout the day with the longest lasting about 45 minutes. The maximum frequency of spasms in a cluster was 6 to 7 per minute. On average, CS was having 6 to 7 clusters a day, the maximum being 8 per day. She was initially treated with temazepam, but it was not helpful. Within a month, the frequency of these spasms had increased to up to 60 per day.

Electroencephalography (EEG) at 23-1/2 months confirmed seizure activity. The report read “A very high amplitude irregular slow background with multifocal high amplitude sharp waves and spikes. Very abnormal, nearly hypsarrhythmic record. Consistent with epileptic spasms.” CS also developed episodes of Generalized Tonic Clonic Seizures (GTCS) between 24 and 27 months. She was diagnosed with TSC at 24 months of age by a paediatric neurologist according to published guidelines. DNA analysis confirmed a TSC1 mutation. Magnetic Resonance Imaging (MRI) brain at 26 months showed multiple tubers in left frontal area characteristic of TSC.
Repeat EEG at 25 months showed some improvement, with no hypersrrhythmia but frequent asynchronous spikes and sharp waves with frontal emphasis and no marked asymmetry. Seizure control was difficult to obtain at first. After various medication changes, seizures responded best to a combination of vigabatrin and clobazam. Episodes of GTCS stopped completely by 26 months of age, epileptic spasms by 30 months and staring episodes by 31 months. Repeat EEG at 36 months was abandoned because of child’s lack of cooperation.

CS’ epilepsy was rated on the Childhood Epilepsy Severity Scale (Humphrey et al., 2008). This scale uses 6 epilepsy related variables including frequency of seizures, time period over which seizures occur, response to treatment, number of anticonvulsants used, status epilepticus and number of seizure types. These variables are scored from 0-3 (3=greatest severity) to generate scores representing the severity of epilepsy in the current, first and second years of life. CS’s score on this scale at 73 months of age at her most recent assessment by our team at the Michael Rutter Centre (MRC) was 1 (due to prescribed anticonvulsants). She had no active seizures then. This score was much lower than her score of 13 in the 2nd year of life when her seizures were poorly controlled. The parents report that CS has never had any episodes of status epilepticus.

2.3 Regression of Skills
CS started losing skills after the onset of epileptic spasms at 22 months of age. The regression was obvious within the first few days of the onset of spasms and the overall regression happened over a period of 1-2 months. CS lost her verbal skills first. She stopped talking in sentences within the first couple of days after the onset of spasms. Within a month, her only words left were “Mama and Dada”. CS also lost her self help and play skills over a period of 1 month. Following the onset of GTCS, CS became quite clumsy, but did not develop any localized weakness. She would drop things and fall over more often than before. Although CS’s gait appeared normal when assessed, her parents reported that she continues to be slightly clumsy in her gait, by which they meant that she tends to fall over because she trips over obstacles in her way. CS also lost her sense of danger and became very impulsive. As reported by her parents, CS had no obvious further regression after subsequent seizure episodes. However, her development has been very slow since then. The initial regression was confirmed by clinical assessments at 28, 30, 32, 35 and 36 months by a paediatric doctor and Play Specialist. These assessments did not use any standard developmental assessment tools but nevertheless, highlighted that CS had lost many skills which she had acquired prior to the development of seizures including verbal skills, use of conventional body gestures, use of eye contact for communication, imaginative play and self-help skills. Imaginative play was replaced with engagement in repetitive play.

2.4 Assessments at the MRC and Addenbrooke’s hospital
CS has had 3 detailed multidisciplinary assessments. She was seen at the MRC twice, at 38 months and at 73 months of age and was seen once at the department of child psychiatry at Addenbrooke’s hospital, Cambridge at 54 months of age. The assessments have included detailed clinical interviews with parents and various well validated measures including Checklist of Autism in Toddlers (Baron-Cohen et al., 2000), Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and Autism Diagnostic Observational Schedule-Generic (ADOS-G) (Lord et al., 2000). The ADOS-G scores were calculated using the revised ADOS algorithm (Gotham et al, 2007) on “module 1, some words”. The composite scores (total of scores in all the 3 domains) were used for diagnosis. Cognitive development was assessed using Mullen’s Scales of Early Learning (Mullen, 1995) and
Vineland’s Adaptive Behaviour Scale (ABS) (Sparrow et al., 1984) was used to get her mother’s view of her development. The results of the assessment at age 73 months are summarised in table 1. CS’ performance on the Mullen’s would indicate that she was functioning at approximately 30 months level in all areas. Parental responses on the Vineland’s ABS indicated that CS remained significantly impaired in her adaptive and social functioning.

Table 1 Developmental age of CS according to test results at 73 months

<table>
<thead>
<tr>
<th>Domain</th>
<th>Vineland’s ABS</th>
<th>Mullen’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive language:</td>
<td>17 months</td>
<td>19 months</td>
</tr>
<tr>
<td>Expressive language:</td>
<td>21 months</td>
<td>29 months</td>
</tr>
<tr>
<td>Visual reception:</td>
<td>23 months</td>
<td></td>
</tr>
<tr>
<td>Socialisation (interpersonal relationships):</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td>Daily living skills:</td>
<td>12-28 months</td>
<td></td>
</tr>
<tr>
<td>Gross motor:</td>
<td>29 months</td>
<td></td>
</tr>
<tr>
<td>Fine motor:</td>
<td>46 months</td>
<td>34 months</td>
</tr>
</tbody>
</table>

Results indicate CS is within the ‘moderate to severe intellectual disabilities’ range which is referred to as ‘moderate to severe mental retardation’ in the International Classification of Diseases 10th edition (ICD-X). This definition is accepted by the World Health Organization (WHO) (World Health Organization, 1992). On comparing these with the previous assessment findings 19 months earlier, it appeared that CS had made little progress in her skills. She displayed typical and marked social and communication difficulties that met criteria for childhood autism on both ADI-R and ADOS-G (Figures 1 and 2). As CS’ epilepsy was well controlled as rated on the Childhood Epilepsy Severity Scale, her continued social and communication difficulties are unlikely to be a manifestation of persistent on-going seizures.

At the time of the above mentioned assessments, CS was receiving routine community services for her developmental difficulties but no specific early interventions for ASD.

3. Case Vignette 2

3.1 Early Development
This child, here after referred to as LH, was born at 42 weeks by normal vaginal delivery. Her mother had some minor vaginal bleeding at 15 and 20 weeks. There were also some concerns regarding ultrasound findings of the foetal heart and kidney on routine scan, but these subsequently resolved. LH walked at 12½ months. She said her first words at 9 months. At 20 months, LH had 50 words and was imitating animal noises. She was not yet talking in phrases or toilet trained by 22 months of age, which is when she first developed seizures.

3.2 Initial Seizure Presentation
The initial seizure episodes were characterized by LH staring blankly and then vomiting. These soon progressed to include recurrent symmetrical upward jerks of her arms, along with head nods. Clinically, these appeared like epileptic spasms. The EEG at the time showed epileptic activity and was severely abnormal, but the characteristic hypersarrhythmic pattern was not seen. Epileptic spasms came in clusters of 5-6, within a 2-3 minute period. In addition to these, there were also 3
episodes of GTCS spread over few days within a month of the onset of above described symptoms. At 23 months of age, an EEG showed almost continuous epileptiform activity and the child was consequently commenced on sodium valproate and clobazam. MRI brain scan at 24 months showed multiple tubers bilaterally and 3 very small sub-ependymal nodules, one arising in the head of the right caudate nucleus, one adjacent to the trigone of right lateral ventricle and one adjacent to the left lateral ventricle. The diagnosis of TSC was formally made at this point. LH was found to have missense variant of TSC2 gene.

3.3 Regression of Skills
According to contemporaneous reports and history from parents, developmental regression occurred almost overnight after the first GTCS between age 22 and 23 months. While she had a vocabulary of 50 words previously, after the seizure onset vocabulary diminished to babbling. “Mama” and “Dada” were her only remaining words that were used meaningfully and consistently. Her understanding of spoken language also regressed. She became very withdrawn and rarely showed any meaningful interaction. LH also lost her self-help skills and became completely dependent for care. At age 24 months, LH had a speech and language assessment that showed moderate expressive language delay (approximately 12 months).

3.4 Seizure Control and Correlation with Regression
Seizure control was difficult to obtain. An EEG at 24 months of age showed frequent and at times continuous slow spike and slow wave discharges, which are described in Lennox Gastaut syndrome. Use of prednisolone improved both the EEG and her seizures. Within 2-3 days of starting prednisolone, LH started showing remarkable improvement in her speech and regained almost 70% of previous expressive speech in the next 3 months. Her speech comprehension also improved. As the dose of prednisolone was decreased and stopped after 3 months, lamotrigine was introduced and given along with valproate and clobazam. Following this, her seizures again worsened. Epileptic spasms and staring episodes became more frequent and there were 2 or 3 GTCS episodes in the next 2 months. She also developed daily Complex Partial Seizures (CPS) in the form of smiling and extending her left hand out. Based on the contemporaneous reports and history from parents, her language again showed regression, but not as much as before. Clobazam was withdrawn due to its sedative side effects.

At the age of 31 months, her EEG showed sharp and slow wave complexes, more frequent over the right temporal region. Prednisolone was again added to cover this period. When it was withdrawn after 3 months, LH showed no further regression. However, her epilepsy remained difficult to control over the next 18 months.

EEG at 42 months was reported as showing “frequent epileptiform discharges with anterior and left sided emphasis but no clear focal abnormality”. At that time, LH had influenza and her speech appeared to have regressed temporarily for a week, but later returned to its previous state. Telemetry done at 44 months “showed numerous clusters of typical spasms that were associated with ill-formed sharp component over the left preceded by an anteriorly distributed sharp wave over the right”. The interictal EEG showed multifocal abnormalities particularly over left frontal, right centro-temporal and right parietal regions. During this period valproate and topiramate were prescribed but withdrawn because of poor response, while vigabatrin was stopped because of
concerns regarding its potential visual side effects. From 49 months of age, LH continued to take only lamotrigine.

LH has exhibited no epileptic spasms since 48 months of age. Between 30 months to 60 months, she continued to have staring episodes and CPS. Her CPS were of different types (including smiling and extending her left hand out with a dazed look on her face; seeking out her parents, clinging to them and then becoming unaware of her surroundings and making groaning noises). These episodes occurred almost daily. While her CPS was very frequent, they were rarely followed by secondary GTCS (about 2/year). Though LH gradually improved with regards to speech, social skills and self help skills, she developed very slowly.

LH had developmental assessments done on Griffiths Mental Developmental Scales (Griffiths, 1954) at 29, 34 and 42 months of age that confirmed the slow developmental progress (see table 2). At age 43 months, LH had a language assessment on Reynell Developmental language scales III (Reynell et al., 1990) that found her language comprehension to be 22 months while language expression was 26 months.

**Table 2** LH’s Developmental assessments on Griffiths Mental Developmental Scales at age 29, 34 and 42 months

<table>
<thead>
<tr>
<th>Domain</th>
<th>Developmental level at 29 months</th>
<th>Developmental level at 34 Months</th>
<th>Developmental level at 42 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locomotor:</td>
<td>36 months</td>
<td>32 months</td>
<td>34 months</td>
</tr>
<tr>
<td>Personal/Social:</td>
<td>30 months</td>
<td>30 months</td>
<td>34 months</td>
</tr>
<tr>
<td>Hearing and Speech:</td>
<td>20 months</td>
<td>22.5</td>
<td>23.5 months</td>
</tr>
<tr>
<td>Eye hand co-ordination:</td>
<td>21.5 months</td>
<td>24 months</td>
<td>28 months</td>
</tr>
<tr>
<td>Performance:</td>
<td>36 months</td>
<td>30 months</td>
<td>30 months</td>
</tr>
<tr>
<td>Practical Reasoning:</td>
<td></td>
<td></td>
<td>30 months</td>
</tr>
</tbody>
</table>

LH was seizure free between 62-78 months, but then the seizures resurged. They were characterized by 1-2 episodes of CPS per day with occasional episodes of secondary GTCS (about 2-3 over the next 2-3 weeks). An EEG done at 78 months of age read “Frequent runs of sharp and slow wave activity in right posterior temporal/occipital regions. These runs of sharp and slow waves at times became generalised and mainly seen at sleep”. This may mean that she was having seizure activity during sleep. An increase in the dose of lamotrigine led to better seizure control within the next 3-4 weeks. Since then, her seizures have followed a similar pattern. She continues to have recurrent staring episodes diagnosed as CPS, with occasional secondary generalization. The staring episodes happen about once every month. The CPS (with or without secondary generalization) tends to recur when LH is unwell. The GTCS episodes mostly have to be terminated by using per rectal diazepam or midazolam. They used to last for an average of 20 minutes but now are controlled earlier as parents promptly use rescue treatment. The longest episode of GTCS lasted 45 minutes at 84 months of age. LH’s last episode of CPS with secondary generalization was at 114 months of age. LH has not experienced any further regression but has shown very delayed acquisition of skills.
LH’s epilepsy was rated on the Childhood Epilepsy Rating Scale. Her score at age 127 months was 1 (due to being on anticonvulsants) whereas her score when her seizures were poorly controlled in the 2nd year of her life was 17. Her 1st year score was 0 as her epilepsy only started in the 2nd year. Her ongoing difficulties are unlikely to be the product of continuing seizures.

3.5 Assessments at the MRC
LH was seen at the MRC at 79 and 127 months of age. The assessments have included detailed interview with parents and various well validated measures including Social and Communication Questionnaire (SCQ) (Rutter et al., 2003), ADI-R and ADOS-G. The ADOS-G scores were calculated using the revised ADOS algorithm (Gotham et al., 2007) on “module 2, older (5-12 years)”. The composite scores (total of scores in all the 3 domains) were used for diagnosis. Development and Well Being Assessment (DAWBA) (Goodman et al., 2000) was used to obtain information about other areas of development and behaviour. Cognitive development was assessed on Wechsler Intelligence Scales for Children - 4th edition (WISC-IV) (Wechsler, 2003) and The Vineland’s ABS (see tables 3 and 4).

Table 3 LH’s performance on the WISC-IV at 125 months

<table>
<thead>
<tr>
<th>Domain</th>
<th>WISC IV Percentile Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Comprehension Index:</td>
<td>0.1</td>
</tr>
<tr>
<td>Perceptual Reasoning Index:</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Working Memory Index:</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Processing Speed Index:</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Full Scale IQ:</td>
<td>&lt;0.1 (IQ ~40)</td>
</tr>
</tbody>
</table>

Table 4 Developmental age of LH according to parental responses to Vineland’s ABS at 125 months

<table>
<thead>
<tr>
<th>Domains of Vineland’s ABS</th>
<th>Developmental Age in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Play and Leisure Time:</td>
<td>104</td>
</tr>
<tr>
<td>Receptive language:</td>
<td>94</td>
</tr>
<tr>
<td>Domestic Daily Living Skills:</td>
<td>74</td>
</tr>
<tr>
<td>Coping Skills:</td>
<td>72</td>
</tr>
<tr>
<td>Written Language:</td>
<td>71</td>
</tr>
<tr>
<td>Interpersonal Relationships:</td>
<td>68</td>
</tr>
<tr>
<td>Community Daily Living Skills:</td>
<td>64</td>
</tr>
<tr>
<td>Expressive language:</td>
<td>48</td>
</tr>
<tr>
<td>Personal Daily Living Skills:</td>
<td>41</td>
</tr>
</tbody>
</table>

Results at age 125 months indicate LH has ‘moderate intellectual disabilities’, which is referred to as ‘moderate to severe mental retardation’ in the International Classification of Diseases 10th edition (ICD-X). This definition is accepted by the WHO (World Health Organization, 1992). There was no discrepancy between the verbal and performance IQ. Parental responses on the Vineland’s ABS at 125 months indicated that LH remained significantly impaired in her adaptive and social functioning. When comparing these with the previous assessment findings at 79 months, it appeared that LH had made progress in all areas except her socialisation skills, which seem to have
plateaued. The progress was probably in relation to the improved control of her seizures, which was evident from the ratings on the Childhood Epilepsy Rating Scale.

Figures 1 and 2 show the ADI-R and ADOS-G scores for both the cases in this report and illustrate the differences between them. LH had algorithm scores above cut off for a diagnosis of autism on social and communication subscales of ADI-R for the age 4-5 year period. However, she was below cut off for an ASD diagnosis on the ADOS-G administered both at 79 and 127 months of age. The ADOS-G scores for LH in the figure 2 are from the assessment done at 127 months of age only; however these are very similar to the one administered at 79 months. It was concluded that although LH exhibited several autistic like social communication impairments, she did not meet research diagnostic or clinical criteria for a diagnosis of autism or ASD at later follow-up.

At the time of the above mentioned assessments, LH was receiving routine community services for her developmental difficulties but no specific early interventions for ASD.

**Figure 1.** ADI-R scores: Numbers on the Y-axis represent the ADI-R scores while the X-axis lists the ADI-R domains for CS (Reciprocal Social Interaction; Non verbal communication; Restricted, Repetitive and Stereotyped Patterns of Behaviour) and LH (Reciprocal Social Interaction; Verbal communication; Restricted, Repetitive and Stereotyped Patterns of Behaviour). For CS, scores were above cut off for autism on all the domains whereas for LH, scores were above cut off for social and verbal domains.

Social = Reciprocal Social Interaction
Non verbal = Non verbal communication
Verbal = Verbal communication
Rep. beh = Restricted, Repetitive and Stereotyped Patterns of Behaviour
Figure 2. ADOS-G scores: Numbers on the Y-axis represent the ADOS-G scores while the X-axis lists the ADOS-G domain scores (Language and Communication; Reciprocal Social Interaction; Restricted and Repetitive behaviours; Composite) for CS and LH, using the revised ADOS-G algorithm, “module 1, some words” for CS and “module 2, older (5-12 years)” for LH. The composite score was above cut off for ASD for CS but not for LH as shown in the figure. The composite score was also above cut off for a diagnosis of Autism for CS (cut off score 12; not shown in the figure).

Comm. = Language and Communication
Social = Reciprocal Social Interaction
Rep. beh. = Restricted and Repetitive behaviours
Comp. = Composite

4. Discussion

These case reports add further to the existing reports documenting regression in development following the onset of seizures in children with TSC (Deonna et al., 1993; Humphrey et al., 2006). The cases reported here are striking in that the regression occurred quite late on in development and towards the end of the second year in both instances. Deonna and colleagues (Deonna et al., 1993) had described 2 cases diagnosed with TSC. One of her cases showed late onset regression beginning at about 22 months of age while the other case regressed around 13 months of age. The regression occurred in association with the onset of seizures. In the other published case (Humphrey et al., 2006), the regression occurred between 21 and 24 months of age. The similarity in the age of onset of the regression between the cases in this report and that described in 2 of the 3 cases in the above mentioned reports (Deonna et al., 1993; Humphrey et al., 2006) is notable, but may be coincidental. It is possible that there is some key event in brain development at about this time that may be pertinent. Apart from the timing of the regression, the two cases in this report are
interesting in terms of the pattern of regression. In the first case there was a clear and dramatic loss of skills and the emergence of an autistic syndrome with no apparent recovery even after the epilepsy was controlled. In the second case, the initial regression was followed by partial recovery following treatment with steroids, but further loss of skills occurred in association with worsening control of the seizures and episodes of status epilepticus. Also, the regression in this case mainly affected intellectual abilities and there was much less and subtler emergence of autistic behaviours.

These cases and the previous reports of cases of tuberous sclerosis with developmental regression are particularly interesting because of the close temporal relationship between the onset of seizures and developmental regression. This is suggestive of a form of epileptic encephalopathy.

Both the children reported here developed epilepsy before 2 years of age and both presented clinically with epileptic spasms along with other types of seizures. CS had a hypsarrhythmic EEG, but the EEG in LH was not reported as typical of hypsarrhythmia. Clinically, the triad of epileptic spasms, hypsarrythmia and arrest of psychomotor development that was seen in CS has been described in West syndrome, a type of epileptic encephalopathy although it commonly has an onset before the age of 1.

In LH’s case, the evolution of the seizures and the EEG findings with frequent and at times continuous slow spike and slow wave discharges are consistent with Lennox Gastaut syndrome, a type of epileptic encephalopathy. Although there is no clear consensus on the features of Lennox Gastaut syndrome, LH does have a number of clinical characteristics described in this syndrome. These include polymorphic seizures, neuropsychological decline, episodes of status epilepticus and EEG abnormalities. Nearly all (85–92%) children affected by Lennox Gastaut syndrome have severely impaired cognition and behaviour (Panayiotopoulos, 2005).

Although epilepsy constitutes one of the key potential risk factors for developmental regression in TSC, several lines of research indicate that other factors need also be considered. For example, there is evidence that heterozygous TSC1+/− and TSC2+/− mice who neither have cortical tubers, nor seizures, still show impairments in hippocampal learning and behaviour (Goorden et al., 2007; Ehninger et al., 2008; 2012). Moreover, the cognitive and behavioural changes reported in TSC2+/− mice can be reversed by treatment with rapamycin, an mTOR inhibitor, suggesting that the abnormalities arise from dysregulation of mTOR signalling (Ehninger et al., 2008). In addition, recent work has indicated that TSC2 haploinsufficiency in mice results in changes in the ephrin-Eph receptor system and abnormalities in the control of axon guidance within the visual system (Nie et al., 2010). The latter findings indicate that there may be more widespread abnormalities in axon growth and guidance and hence ‘connectivity’ between brain regions and this might lead to intellectual and behavioural deficits. However, to be relevant to the developmental regression reported here, these genetics effects would have to be developmentally regulated or there would need to be some form of gene-environment interaction (Ehninger et al., 2012).

Regarding the role of epilepsy, Bolton et al. (2002) has postulated that the site of epileptic discharges may be relevant with respect to the emergence of ASD. In interpreting data from his study he proposed that epileptiform discharges arising from tubers in the temporal lobes, and possibly other regions within the ‘social’ brain, may contribute to the development of autistic symptoms if the onset of discharges occurred in the first 3 years of life (mainly within 18 months).
and during a critical period of development within which social cognitive representations are instantiated. Bolton et al. (2002) found an association between epileptic spasms and development of autism, but the association was dependent on the origin of discharges within the temporal lobes and the age of seizure onset. Other studies (Gutierrez et al., 1998) have found that epileptic spasms increase the risk of developing autism in TSC but that they are neither necessary nor sufficient for development of autism (Hunt and Dennis, 1987). Others have noted that hypsarrhythmia on EEG is associated with the development of ASD in TSC (Baker et al., 1998). The association between epileptic spasms and autism has also been seen in children without TSC. For example, two-thirds of children with West syndrome usually develop severe cognitive and psychological impairment (Panayiotopoulos, 2005). Autistic behaviour, hyperkinetic syndrome and psychiatric disorders may even be seen in otherwise normal patients with a previous history of epileptic spasms (Panayiotopoulos, 2005). Clearly epilepsy and epileptic encephalopathy need to be considered in all cases that show developmental regression.

CS did not show evidence of temporal lobe tubers or epileptiform activity arising from temporal lobes, but she did have prolonged treatment resistant epileptic spasms and hypsarrhythmia. Therefore, it is possible that the prolonged duration of epileptic spasms and hypsarrhythmia in CS may have placed her at a higher risk of development of autism (Baker et al., 1998). In contrast, LH had bilateral temporal lobe tubers and epileptic spasms, but much fewer autistic symptoms. It is possible that her developmental outcome was partially influenced by early treatment with steroids and subsequent episodes of status epilepticus.

5. Conclusion

The two cases described in this study add to the existing reports documenting regression in development following the onset of seizures in children with TSC. Evidently, the risk pathways to developmental outcome in TSC have not yet been fully mapped. In the future however, it is clear that the investigation of the risk processes will require prospective longitudinal studies of children with TSC before the onset of seizures.

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