

# **Autism, ADHD and parent-reported behavioural difficulties in young children with epilepsy**

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**Abstract**

**Purpose:** To provide data on the prevalence of Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), and parent reported behaviour difficulties in young children with epilepsy, and to compare results with children with neurodisability (neurodevelopmental/neurological difficulties) without epilepsy.

**Method:** Children with epilepsy (1-7 years, n=48) and children with neurodisability (1-7 years, n=48) matched for gender, chronological and developmental age underwent psychological assessment. Parents completed measures of behaviour including the Strengths and Difficulties Questionnaire (SDQ). DSM-5 diagnoses of ASD and ADHD were made at consensus case conferences. Factors associated with child behaviour were analysed using linear regression.

**Results:** Of the children with epilepsy, 18% met ASD criteria and 40% met ADHD criteria (corresponding figures in the non-epilepsy group were 33% and 27%). A large proportion (76%-78%) in both groups scored in the at-risk range on the SDQ and frequently had difficulties across multiple behavioural domains. Children with epilepsy had more concerns expressed regarding attention and mood. None of the epilepsy factors were significantly associated with scores on the behavioural measures.

**Significance:** Young children with epilepsy had a very high level of parent reported behavioural difficulties and a high risk for ADHD and ASD highlighting the need for comprehensive multidisciplinary assessment. Behavioural concerns were not greater than for other children with non-epilepsy related neurodisability with the exception of attention and mood. Epilepsy related factors were not associated with child behaviour, suggesting that seizures per se do not confer a unique risk for behavioural difficulties.

**Keywords:** epilepsy, children, ADHD, autism, behaviour

## **Introduction**

Difficulties with neurodevelopment and behaviour are frequently reported in children with epilepsy<sup>1</sup>. The difficulties experienced by the children are greater than that experienced by children with other non-neurological conditions<sup>2</sup> and have often a greater impact on Health Related Quality of Life (HRQOL) than seizures<sup>3</sup>. In school-aged children the prevalence of behavioural comorbidities have been described<sup>1</sup>. There is however, limited data on behavior in younger children with epilepsy<sup>4</sup> including the presence of Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). Additionally, there are limited data on whether behavioural profiles in children with epilepsy differ from those of children without epilepsy but with other neurodevelopmental or neurological conditions.

Knowledge of the prevalence of difficulties with behavior as well as the presence of ADHD and ASD is important with respect to understanding the impact of epilepsy on neurodevelopment. It may have implications for both intervention and prognosis and support the provision of services that better addresses HRQOL in this population. Comparing children with epilepsy with children without epilepsy but with other neurodevelopmental or neurological conditions could determine whether the behavioural profile of children with epilepsy is unique. This in turn may have implications for management but also for understanding the biological underpinnings of behavioural difficulties in young children with early onset epilepsy.

The Sussex Early Epilepsy and Neurobehaviour (SEEN) project focusses on the psychosocial impact of epilepsy on young children and their parents. We have previously described recruitment in the study<sup>5,6</sup>. Fifty-three children with epilepsy were identified in the study area and 48 children subsequently underwent psychological assessment. We also recruited a comparison group of children with non-epilepsy related neurodisability. All of these children had neurological or neurodevelopmental difficulties requiring ongoing support. There were no significant differences between the epilepsy group and the neurodisability group with respect to gender, age, being on the special educational needs register, presence of cerebral palsy or developmental quotient<sup>5</sup>. We have previously reported that 71% of children with epilepsy in the SEEN study have delayed global development (<2SD), 56% showed significant deficits (<2SD) in adaptive behavior<sup>5</sup> and that 81% of the children with epilepsy scored in the at-risk range on a measure of parent reported sleep<sup>6</sup>.

The aim of the current study was to determine the prevalence of ADHD, autism and significant behavioural difficulties among young children with epilepsy. A secondary aim was to compare behavioral profiles in the children with epilepsy with a developmental, age and gender matched group of children with neurodisability without epilepsy. An additional aim was to consider factors including demographic and epilepsy related factors associated with the behavioral difficulties.

## **Methods**

We have previously described recruitment in the SEEN study<sup>5,6</sup>. In short we aimed to identify all children with epilepsy (a history of 2 or more unprovoked epileptic seizures more than 24 hours apart) born between the years 2008 and 2014 in the RH10-RH14 postal districts of the south of England. The study period was from September 30th 2014 to February 29th 2016. All of the children had undergone EEG investigation and had epilepsy confirmed by a paediatrician or paediatric neurologist. The children

needed to have reached their first birthday during the study period in order to be included and subsequently assessed. Primary caregivers of the children with epilepsy were approached in person or sent a letter and asked to complete an interest form if they wished to find out more about the study. Interested primary caregivers were met by psychologists on the research team to discuss the study and the possible participation of their child.

After a child with epilepsy was enrolled in the study, primary caregivers of children with comparable attributes (in terms of age, gender and developmental level) without epilepsy, attending the same paediatricians in the same geographical area were approached. All of these children had neurological or neurodevelopmental difficulties requiring ongoing support.

#### Medical assessment

All the children were individually assessed and examined by an experienced paediatrician. At least one parent of each enrolled child was interviewed regarding the child's early history, about factors related to the child's epilepsy, and about overall level of functioning and behaviour.

#### Psychological assessment and parent completed measures of behaviour

Children in both groups were assessed at home by one of the two research psychologists between the period November 1<sup>st</sup> 2014, and April 30<sup>th</sup> 2016. The child's primary caregiver completed the following instruments regarding their child's behaviour: Modified-Checklist for Autism in Toddlers (M-CHAT)<sup>7</sup>, the Strengths and Difficulties (SDQ) questionnaire<sup>8</sup>, the ESSENCE-Q-REV<sup>9</sup> the Autism Spectrum Screening Questionnaire (ASSQ)<sup>10</sup> and the ADHD-RS-IV<sup>11</sup>. In addition to this, a semi-structured five-item observation of joint attention at the home visit was used by the psychologist. This has previously been used in a study of young children with autism and focusses on early joint-attention behaviors<sup>12</sup>.

The M-CHAT<sup>7</sup> is a screening instrument for ASD and contains 23 items including a 6 items 'critical' subscale. It is usually used for children between 16 and 30 months but has been used with older children including children with epilepsy<sup>13</sup>. The total score gives an indication of whether a child needs a more comprehensive assessment for ASD.

The ESSENCE-Q-REV questionnaire contains 11 items concerning the child's neurodevelopment<sup>9</sup>. Respondents are asked if they (or anybody else) have been concerned for more than a few months regarding the child in 11 developmental/behavioral domains. The response options are Yes (2 points), Maybe/A little (1 point) or No (0 points). The total score ranges from 0-22.

The parents of all the children completed the ESSENCE-Q-REV and M-CHAT.

If the child was aged 2 years or older (38 children with epilepsy, 32 children without epilepsy), the primary caregiver completed the SDQ. The SDQ contains 25 questions in the following 5 areas: emotional symptoms, conduct problems, hyperactivity, peer relationship problems and prosocial behavior<sup>8</sup>. As well as in each of the five areas it is also possible to calculate a total score. The SDQ has been found to be useful with regard to the identification of behavioral difficulties in preschool children<sup>14</sup>.

For children 4 years and older and with a developmental quotient >34 (epilepsy n=25, controls n= 23) parents completed the ASSQ or the ADHD-RS-IV. The ASSQ is a screening instrument for ASD which consists of 27 items on a three-point scale: not true (0), 'sometimes true' (1), and 'certainly true' (2)<sup>10</sup>. The ADHD-RS-IV is an 18-item questionnaire based on the diagnostic criteria for ADHD as described in *DSM-IV*<sup>15</sup>. The ADHD-RS-IV includes Inattention and Hyperactivity-Impulsivity subscales and a total score. Parents are asked to rate the child with respect to their behaviour over the previous 6 months.

The joint attention observation used in the current study has previously been used in a study of young children with autism and focusses on early joint-attention behaviors<sup>12</sup>. Each item was scored as pass (1) or fail (0) based on the psychologists' clinical judgment. All children underwent this observation.

### Consensus clinical diagnoses

Consensus clinical diagnoses of autism and ADHD were made with respect to relevant DSM-5<sup>16</sup> criteria based on consensus diagnosis by one of the two study psychologists (C.R.), a community paediatrician (P.A.), and a very experienced child and adolescent psychiatrist (C.G.). The consensus diagnostic process involved a review of children's developmental/medical history based on case/medical notes, results of administered standardised screening measures and developmental assessments, and home based observations by study psychologist. Children under 2 years of age were not considered for a diagnosis of autism and children under 4 years of age were not considered for a diagnosis of ADHD. This meant that 45 out of 48 (94% of the total) children with epilepsy and 39 out of 48 (81% of the total) children with non-epilepsy related neurodisability were considered for a diagnosis of autism. With respect to ADHD, the equivalent proportions were 35 of 48 (73%) in the epilepsy group and 30 of 48 (62%) in the non-epilepsy related neurodisability group.

The assessment of global development was undertaken with the Griffiths Mental Development Scales (GMDS)<sup>17</sup> or the Griffiths Mental Development Scales-Extended Revised<sup>18</sup>. Child sleep was assessed by the Child Sleep Habits Questionnaire (CSHQ)<sup>19</sup> and parental mental health by the Depression Anxiety and Stress Scale (DASS)<sup>20</sup>.

Information on the child's epilepsy was extracted using a proforma. Two paediatric neurologists (LD and KD) independently classified seizures as generalized or focal with disagreements being decided by a third neurologist (RS). Aetiology of epilepsy was classified by a paediatric neurologist (HC) according to ILAE 2017 classification of epilepsies<sup>21</sup>.

Deprivation was determined by the Index of Multiple Deprivation 2015 rankings (Department of Communities and Local Government, English Indices of Deprivation; retrieved from <http://imd-by-postcode.opendatacommunities.org/> [accessed 15th December 2016]). Lower scores are associated with lower deprivation. Home postcodes were used to establish the Index of Multiple Deprivation 2010 ranking of each family.

### *Analysis*

The analyses were done with IBM SPSS version 25.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

Comparisons between the epilepsy group and the neurodisability group on the behavioural screening measures were undertaken with t-tests/chi-square analyses. Where significant differences were found between the two groups, results are reported before and after Bonferroni adjustment for multiple comparisons.

Linear regression analyses were performed with respect to possible factors associated with the total scores on the M-CHAT, ESSENCE-Q and SDQ in the epilepsy sample. The factors included as potential predictors in the linear regressions were gender (male vs. female), child's age (in years), deprivation (based on multiple deprivation index data), age of onset of first seizure (in years), seizure frequency (monthly or more often vs. less often) and current treatment (1 AED (monotherapy) vs 2 AEDs or more (polytherapy)). The predominant seizure type was either generalized or focal. Developmental Quotient was based on results from the GMDS/GMDS-ER. The sleep score was based on scores from the CSHQ and maternal and paternal mental health was based on total score on DASS. All independent variables were first tested by univariable linear regression. The factors associated at the  $p < 0.100$  level were included in multivariable analysis. Alpha level for univariable and multivariable analysis was  $p < 0.05$ .

### **Ethics Approval**

This study received approval from the Westminster Research Ethics Committee. It was also registered with the collaborating hospital primary care organisation: Sussex Community NHS Trust.

### **Results**

During the study period 53 children with epilepsy were identified in the study area who met eligibility criteria. Parents of 48 of the 53 (89% ascertainment) agreed to take part and subsequently underwent psychological assessment. There were no significant differences between the participants and non-participants with epilepsy on any of the available characteristics which were age ( $p=0.778$ ), gender ( $p=0.658$ ), special school placement ( $p=0.959$ ), presence of autism ( $p=0.262$ ) or presence of cerebral palsy ( $p=0.478$ ). In the comparison group, 56 parents returned an interest form and 48 agreed to participate.

The main characteristics of the 48 children with epilepsy and the 48 children with non-epilepsy related neurodisability in the SEEN study are shown in Table 1.

### **DSM-5 diagnoses of Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD)**

The results of the consensus diagnostic process with respect to DSM-5 ASD are shown in Figure 1.

Eight (18%) of the eligible children ( $n=45$ ) with epilepsy met DSM-5 diagnostic criteria for ASD. The equivalent figure in the non-epilepsy related neurodisability group was 16 (41%) of eligible children ( $n=39$ ).

The results of the consensus diagnostic process with respect to DSM-5 ADHD are shown in Figure 2.

Fourteen (40%) of the eligible children (n=35) with epilepsy met DSM-5 diagnostic criteria for ADHD. The equivalent figure in the non-epilepsy related neurodisability group was 8 (26%) of eligible children (n=39).

It must be noted that of the children considered for a diagnosis of autism, eight (18%) in the epilepsy group and five (13%) in the non-epilepsy group had a developmental level (a developmental quotient of 34 or less) too low to be considered for a diagnosis of autism. The equivalent percentages for the ADHD diagnostic decision were 23% (n=8) in the epilepsy group and 17% (n=5) in the non-epilepsy group

### **Scores on parent-reported screening measures of neurobehaviour**

Figure 3 shows the percentage of children in both groups who scored in the at-risk cut-off on the SDQ.

Of the children with epilepsy 78% scored in the at-risk range. The corresponding percentage in the non-epilepsy related neurodisability group was 76%.

The scores on measures of neurobehaviour in both groups are shown in Table 2.

There were no significant differences between the two groups with respect to scores on the SDQ (total score or subscale scores), M-CHAT (total score or critical item scores), or ADHD-RS-IV (total score or subscale scores). There was also no significant difference between the groups regarding the proportion of children scoring above the clinical cut-offs on the ADHD-RS-IV. The children in the neurodisability group had significantly higher scores on the ASSQ.

### *ESSENCE-Q-REV*

Scores on the ESSENCE-Q in both groups are shown in table 3:

There was not a significant difference between the groups on the ESSENCE-Q-REV total score (Epilepsy 12.71 vs. Neurodisability 12.23). However, the epilepsy group had significantly higher scores on the attention and mood questions indicating greater parental concerns. These two differences between the groups were not significant after correction for multiple comparisons (adjusted  $p < 0.005$ ).

The results of the regression analysis are in Supplement 1. The only factors significantly associated with the SDQ total score on multivariable analyses were mothers' mental health difficulties ( $p = 0.045$ ) and child sleep difficulties ( $p = 0.045$ ). Greater maternal mental health difficulties and increased child sleep difficulties were both independently associated with increased child behavioural difficulties.

Child age ( $p = 0.022$ ) and developmental level ( $p < 0.001$ ) were independently associated with scores on the M-CHAT. Younger age and lower developmental level were associated with higher scores on the MCHAT.

On the ESSENCE-Q the only factor associated with the total score in the multivariable analysis was child developmental level ( $p > 0.001$ ). Greater developmental impairment was associated with higher scores on the ESSENCE-Q. In the epilepsy group there

were no significant relationships between seizure parameters (age of seizure onset, seizure frequency, use of AEDs, predominant seizure type) and behavioural outcomes.

## **Discussion**

This is one of the first population-based studies of ASD, ADHD and behavioural difficulties in young children with epilepsy. The high rates of difficulties with behaviour including high rates of both ASD and ADHD reported in the study add to our understanding of the comprehensive neurobehavioural impact of early-onset epilepsy and highlight the need for comprehensive early multidisciplinary assessment across multiple domains in this group. The inclusion of a neurodisability group matched for developmental status is novel and allowed consideration of whether epilepsy uniquely confers an increased risk for behavioural difficulties and whether the patterns of behavioural difficulties were different. The increased parental concerns regarding attention and mood in the epilepsy group provide at least some evidence for a unique behavioural profile in young children with epilepsy. The lack of association between epilepsy factors and measures of neurodevelopment and behaviour indicate that treating seizures alone is likely to have limited impact on behaviour for the majority of young children with epilepsy.

There are very few previous studies of ASD and ADHD in young children with epilepsy. A previous population-based study of neurobehavior in school-aged children with active epilepsy employed similar methodology as the current study in the same geographical area and noted that 33% met DSM-IV-TR criteria for ADHD and 21% met criteria for ASD<sup>2</sup>, similar to the rates reported in the current study. ADHD has a very significant negative impact on life quality and educational outcomes<sup>22</sup> and therefore it is important it is identified and appropriately treated. Additionally, there is evidence that symptoms of ADHD can be effectively treated in children with epilepsy<sup>23</sup> even in those with epilepsy and intellectual disability<sup>24</sup>. With respect to ASD a recent systematic review and meta-analysis suggests that younger children with epilepsy are a particularly high risk group<sup>25</sup> highlighting the need for a consideration of the presence of ASD in young children with epilepsy.

Nearly four out of five children in the epilepsy group scored in the at-risk range on a measure of behaviour. The SDQ has previously been employed in a number of population-based studies of older children with epilepsy<sup>26,27,28</sup> and the percentages scoring in the at-risk range on the total score in these studies are lower than the current study. Thus, the findings in the current study indicate that young children with epilepsy are a particular high-risk group with respect to behavioural difficulties. It has previously been suggested that given the very high level of risk in this group, screening for broad-based behavioural difficulties using instruments such as SDQ is unnecessary<sup>29</sup> but that these children require disorder specific screening as part of comprehensive multidisciplinary assessment. Our data support this view given the very high rates of children who scored in the at-risk zone. The results of parent responses on the ESSENCE-Q show that children with epilepsy frequently have problems across multiple neurodevelopmental areas. They are therefore, likely to require support across a range of developmental domains again highlighting the need for comprehensive multidisciplinary assessment.

A previous population-based study of children with newly diagnosed early-onset epilepsy in Scotland found that more 63% children with epilepsy had neurobehavioral



difficulties, significantly more than typical controls (27%)<sup>4</sup>. The current study also found a very high rate of neurobehavioral difficulties in the children with epilepsy but uniquely included a control group with neurodisability without epilepsy. The lack of difference between the epilepsy group and the neurodisability group in the current study across the total scores on the neurobehavioral measures, suggests that seizures do not per se confer a unique risk for the behavioural difficulties for the majority of children. This is in line with a previous study of challenging behaviour in children and young people<sup>30</sup>. Parents of children with epilepsy expressed significantly more concerns with attention and mood suggesting that these areas may be a particular area of need in children with epilepsy. Previous studies have noted that difficulties with attention in epilepsy are particularly common<sup>31,32</sup>. Given that these differences were not significant after correction for multiple comparisons there is a clear need for further research to explore this issue. If there is found to be additional evidence of these being specific difficulties for young children with epilepsy compared with controls matched for development, they may need to be of particular focus in assessment and subsequent psychological interventions.

None of the epilepsy factors considered in our analysis were significantly associated with the measures of neurobehaviour in the current study. This concurs with our previous population-based study in older children<sup>1</sup> and a number of reviews<sup>33,34</sup> which have not found a significant relationship between epilepsy factors and measures of behaviour. This gives weight to the notion that treating seizures alone is not likely to help with the expression of behavioural difficulties for most young children with epilepsy. Maternal mental health and sleep were significant contributors to child behaviour difficulties and thus need to be considered when considering behavioural interventions in children with epilepsy although relationships are likely to be bidirectional in nature.

#### *Directions for future research*

Prospective longitudinal studies are needed to track the course of development and behaviour in young children in epilepsy. Such studies will contribute to a better understanding of the trajectory of the behavioural difficulties and inform the development of interventions and provision of supports in clinical practice. Regarding possible specific difficulties with attention and mood, larger sample sizes are needed to confirm that children with epilepsy are at significantly higher risk for these difficulties and also tease out which children with epilepsy are at highest risk. There is an urgent need to develop and test behavioural interventions for children in this population as studies which have focussed on psychological interventions in childhood epilepsy have focussed predominantly on older children<sup>35,36</sup>.

It is recognized this study has several limitations. Although recruitment of the children with epilepsy was population-based the sample size is small and larger studies of young children with epilepsy are needed. The children in the study were aged between one and seven years and consequently our findings may not be of relevance for younger children or children over seven years of age. The measures of behavior used in the current study are based on parental report only and previous studies have noted differences between teachers and parental report<sup>26</sup>. In particular it is possible that maternal depression, anxiety and stress noted to be high in this population<sup>37</sup> affect ratings of child behaviour. Further, although we used consensus clinical diagnosis based on DSM-5 criteria for the diagnosis of autism and ADHD, which is likely to be

the gold standard, it would have been useful to employ structured diagnostic interviews and/or structured observations for comparative purposes. The M-CHAT has not been validated across the whole age range it was used in this study. Additionally the ASSQ, the additional screener for autism was used only with children four years and older, which may have affected the accuracy of the consensus diagnostic decisions for autism in younger children. The two groups were matched at the group level not at the individual level. This resulted in different proportions of children being considered for the ADHD and ASD diagnoses in each group. The comparison group of children with neurodisability was matched for gender, chronological age and developmental age but is heterogeneous in terms of aetiology and it may be useful to conduct comparisons between children with epilepsy and more homogenous groups to understand the possible differences and similarities in behavioral profiles.

### **Conclusion**

Young children with epilepsy have a very high level of parent reported behavioural difficulties and present with a high risk for ASD and ADHD. Attention and mood may be areas where children with epilepsy have a higher level of need compared with other children with neurodevelopmental or neurological difficulties. Epilepsy related factors are not however, significant contributors to behavioural difficulties in the majority of young children with epilepsy. All young children with epilepsy need comprehensive multidisciplinary assessment and there is a need to develop interventions to treat behavioural difficulties in this population.

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### **Disclosure**

Professor Brian Neville was a Trustee of the George E Neville Foundation. None of the remaining authors have any conflict of interest to declare. 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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