Cognitive and behavioural impulsivity in patients with Juvenile Myoclonic Epilepsy

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Purpose

When patients with juvenile myoclonic epilepsy (JME) present at clinic, the presence of impulsive behaviour and/or poor inhibitory control is often reported yet research findings are variable. The aim of this meta-analysis is to draw together existing research evidence to understand more about cognitive and behavioural impulsivity traits in this patient group.

Methods

• Meta-analyses of 19 articles published between 2007 and 2016
• Studies of patients diagnosed with JME as defined by the International League against Epilepsy
• Overall effect sizes and heterogeneity were measured for
  • the Stroop Task, a measure of cognitive impulsivity based on inhibition of interference (see above) (n=17)
  • scores on questionnaires measuring behavioural impulsivity traits (n=5).
• Separate meta-analyses for the two measures of impulsivity were performed using SPSS scripts and mean effect sizes (ES) were calculated
• For both meta-analyses, homogeneity testing determined the extent to which there was variation in findings between studies using potential indicators.
• Heterogeneity was interpreted using a random effects weighted multiple regression (meta-regression) analysis: potential predictors of effect size were explored for their importance

Results

• Mean Cohen’s d was d = .66 (95% CI 0.41–0.74; z = 8.00; p<.0001) for cognitive impulsivity and d = 1.39 (95% CI 0.64–2.14; z = 9.47; p<.0003) for behavioural impulsivity.
• Both sets of effect sizes were significantly variable (cognitive impulsivity: Q=25; p = .036; behavioural impulsivity: Q=111; p <.0001)
• The high variability of effect sizes associated with cognitive impulsivity was fully explained by an outlier which was removed resulting in homogeneity (Q=13; p = .72) and a slightly reduced but significant overall effect size of .56 (.44–.69) (z=8.8; p <.0001) (see below)
• Although for the behavioural data power was very limited we looked for potential associations and found that the higher the percentage of patients in sample who were medicated with sodium valproate (VPA) the larger the effect size (see below)

Conclusion

We confirm that studies of patients with JME consistently find moderate effect sizes associated with cognitive impulsivity. Effect sizes for behavioural impulsivity are fewer, larger, more wide spread and correlate strongly with proportion of patients in each study taking VPA. This association could be due to a correspondingly a) higher number of male patients and b) higher number of severe cases of JME in those studies with higher effect sizes. Future studies should consider gender and severity effects in their analyses.
Developmental coordination disorder in children with Rolandi 
epilepsy and their siblings
Stuart D. W. Smith, Anna B. Smith and Deb K. Pal

**Introduction**
- Cognitive problems in Rolandi epilepsy (RE) may involve speech, language and literacy (Pal et al., 2010, Smith et 
  al., 2015, Vega et al., 2015).
- These problems are prevalent within families of children with RE and may represent an endophenotype.
- New evidence suggests motor problems or developmental coordination disorder (DCD) may also be present in 
- It is unknown whether DCD is detectable in siblings of children with RE.

**Goals**
1. Using the DCDQ’07 to detect DCD symptoms in children with RE, their siblings and controls.
2. Identify the key problems in motor abilities from subscores.

**Overall scores**
- RE: 8
- Siblings: 1
- Controls: 2

- **Forty-four percent** of children with RE had an indication of DCD.
- This was larger than the controls ($\chi^2=4.58, p=.032$) and siblings ($\chi^2=3, p=.08$).

**Subscores**
MANOVA analysis of subsection scores was not significant ($F=1.8, df=6, 80, p=.109$)
However, post hoc, Bonferroni testing between RE and controls was significant for 
fine motor control ($p=.01$) and coordination ($p=.04$).

**Key problems**
- RE+DCD
- Sibs+DCD
- Con+DCD

**Conclusions**
- There is a high prevalence for the indication of DCD in children with RE compared to controls.
- There appears to be an apparent association with coordination and fine motor skills.
- Indication of DCDQ was less prevalent in siblings.
- Further investigation is needed to see if DCD is related to the 
  RE seizure disorder rather than a component of the endophenotype.
**Introduction**

We established a regional epilepsy genetics service:
- southeast England
- serving a population of 3.5 million.

The service has two components:
- a specialist outpatient clinic
- a molecular diagnostic service.

We evaluated:
- the effectiveness and utility of NGS
- investigation costs
- the patient/referrer experience

![Evelina London Children's Hospital](image)

**Methods**

- **Prospective** observational design over 18 months
- N=96 consecutive patients with primary Dx suspected genetic epilepsy
- Educational workshop for paediatricians

We used:
- Amplexa epilepsy NGS gene panels: 46 – 102 genes
- ACMG variant classification
- MDT clinical interpretation
- ILAE definition of AED resistance

We assessed:
- **Diagnostic yield** by age group
- Family and referrer **satisfaction** survey
- Investigational costs in neonatal epilepsy (n=16)
  - video EEG, MRI, metabolic, single genes

**Results**

**Effectiveness and Utility**

![Figure 1. Demographic breakdown of tested patients](image)

- 60% of patients had ≥ 1 variants
  - 19 benign
  - 16 VUS
  - 23 likely pathogenic

- SCN8a (n=4) and SCN2a (n=3) most common

**Pathogenic variants:**
- SCN8A, SCN2A, SCN1A, KCNQ2, HNRNPU, GRIN2A, SYNGAP1, STXBp1, STX1B, CDKL5, CHRNA4, PCDH19, PIGT

**Turnaround Time:** 21 DAYS

- Overall diagnostic yield 29% amongst AED resistant cases
- Treatment **implications for** 63% with pathogenic variants

**Cost**

- Actual investigation costs neonatal epilepsy €10,171 (range: €5,534 – €16,972).
- Theoretical costs if gene panel first line: €3,083

**Patient/Referrer Experience**

- 100% families would **recommend** to friends and family
- 50% referrers think gene panel **reduces investigations**

**Conclusions**

1. NGS panel has high utility and effectiveness if seizure **onset <2 years**
2. Earlier diagnostic use of gene panel could **cut** investigation costs by 70% or €7,000
3. Turnaround time is **world leading** 21 days vs. median diagnostic delay 3 years
4. Enthusiastic **acceptance of genomic medicine** by referrers and families
High prevalence of intellectual disability, autism, ADHD and diminished adaptive functioning in Doose syndrome (MAE)

Tang S1,2, Smith A2, Parker A1, Agrawal S1, Hughes E1, Lascelles K1, Williams R1, Fallon P1, Robinson R3, Cross JH1, Hedderly T1, Eltze C, Ferré C1, Kerr T1, Desurkar A1, Hussain N2, Kimali M10, Vassallo G11, Whitehouse W2, Goyal S3, Absoud M4, Pal D K1,2

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Introduction and Purpose

- Myoclonic astatic epilepsy accounts for 1 to 5% of childhood epilepsy.
- The epilepsy prognosis is variable and about 1/3 go into remission.
- The neurodevelopmental outcome is unclear and poorly reported.
- We therefore deeply phenotyped MAE cases for neurodevelopmental symptoms of cognitive ability, adaptive behaviour, autism and ADHD symptoms.

Methods

- MAE cases were recruited across UK paediatric neurology centers. Ref: 09/H0713/76
- MAE case definition was based on ILAE 1989 classification:
  1. Usually normal development before onset of epilepsy.
  2. Onset of myoclonic, myoclonic-atomic or atomic seizures between 6 months and 6 years.
  3. Generalised spike wave and/or polyspike wave discharges on EEG.
  4. Absence of related structural cerebral abnormalities on MRI.
- Phenotyping protocol Table 1:

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Assessment Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>Clinical history and examination</td>
</tr>
<tr>
<td>Cognitive ability</td>
<td>WPPSI III, Bayleys III</td>
</tr>
<tr>
<td>Adaptive Behaviour</td>
<td>Adaptive Behaviour Assessment system</td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>Social communication questionnaire (SCQ), Developmental Diagnostic interview (3di)</td>
</tr>
<tr>
<td>ADHD</td>
<td>Conner's Comprehensive Behavior Rating Scale – Parent and Teacher DSM IV/ADHD subscale, T score &gt; 70</td>
</tr>
<tr>
<td>Behavioral screening</td>
<td>Strength and Difficulties questionnaire</td>
</tr>
</tbody>
</table>

Results

- 67 UK MAE cases (49 Male, 18 Females) were recruited.
- Median age of onset 35 months (range 6 to 65), 23 (34%) cases had febrile seizures. Family history of epilepsy in 32 cases (47%).
- Seizures: 100% myoclonic-atomic or atomic, 82% GTCS, 83% myoclonic, 64% absence, 22% tonic and 9% focal seizures.
- Seizure remission of > 2 years was seen in 20 (30%) of cases.
- Low cognitive ability (Figure 2) and adaptive behavior (Figure 3).
- Autism spectrum disorder symptoms were elicited in 20/64 (31%) through the 3di (9/22) and SCQ (16/61).
- ADHD: 21/42 (41%) parents report ADHD with both parent and teacher in 7/52 (13%).
- High scores in behavioural symptoms: emotional symptoms 10/60 (16%), conduct problems 19/60 (31%), hyperactivity/inattention 22/60 (36%), peer relationship problems 29/60 (48%), prosocial behaviour 35/60 (58%). Figure 4 demonstrates multi-morbidity of behavioural symptoms.

Summary:

- One third of MAE patients achieve seizure remission > 2 years.
- MAE patients have significant neurodevelopmental difficulties:
  - 56% have moderate to severe intellectual disability
  - 70% have low adaptive function scores, worst with practical skills
  - 31% have Autism spectrum disorder symptoms
  - 41% have Attention deficit hypertensive disorder symptoms
  - 58% of parents report these difficulties to significant impact on the child and family