Epilepsy and seizures in young people with 22q11.2 deletion syndrome: prevalence and links with other neurodevelopmental disorders

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Summary

Objective: The true prevalence of epileptic seizures and epilepsy in 22q11.2 deletion syndrome (22q11.2DS) is unknown, because previous studies have relied on historical medical record review, rather than direct assessment. Associations of epilepsy with other neurodevelopmental manifestations (e.g. specific psychiatric diagnoses) remain explored.

Methods: The primary caregivers of 108 deletion carriers (x̄= 13.6 years) and 60 control siblings (x̄= 13.1 years) completed a validated epilepsy screening questionnaire. A sub-sample (n=44) took part in a second assessment with interview, prolonged EEG, medical records, epileptologist review. IQ, psychopathology and other neurodevelopmental problems were examined using neurocognitive assessment and questionnaire/interview.

Results: Eleven percent (12/108) of deletion carriers have an epilepsy diagnosis (controls 0%, p=0.004). 57 of the remaining 96 deletion carriers (59.4%) had seizures or seizure-like
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Symptoms (controls 13.3%, 8/60, p <0.001). A febrile seizure was reported for 24.1% (26/108) of deletion carriers (controls 0%, p<0.001). **One deletion carrier was newly diagnosed with epilepsy during the second stage, whilst two more were newly diagnosed with possible absence seizures.** Brief spike-and-slow wave discharges were seen in some of these cases during sleep and upon awakening. A positive screen on the epilepsy questionnaire was more likely in deletion carriers with lower performance IQ (OR=0.96, p=0.018), ADHD (OR= 3.28, p=0.021), autism symptoms (OR=3.86, p=0.004) and motor coordination disorder (OR= 4.56, p=0.021).

**Significance:** Even when accounting for deletion carriers diagnosed with epilepsy, reports of seizures and seizure-like symptoms are common. **These may be ‘true’ epileptic seizures in some cases, which are missed during routine clinical care.** Febrile seizures are far more common in deletion carriers compared to the known population risk. A propensity for seizures in 22q11.2DS is associated with cognitive impairment, psychopathology and motor coordination problems. Future research is required to determine whether this reflects common neurobiological risk pathways or are the consequence of recurrent seizures.

**Key words:** Electroencephalography, seizure semiology, febrile seizure, unprovoked seizure, cognition, psychiatric disorder
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**Key points**

- Over half of young people with 22q11.2DS without an epilepsy diagnosis were reported as having a seizure or seizure-like symptom
- We conducted a second assessment stage in a sub-sample of 44 people including an interview, prolonged EEG, and medical record review
- Epileptic seizures and an epilepsy diagnosis may be missed during routine clinical care in some deletion carriers
- A quarter of young people with 22q11.2DS screened positive for febrile seizures, higher than in previous studies in this population
- Epilepsy, seizures and seizure-like symptoms associated with ADHD, ASD symptoms, motor problems and lower performance IQ in 22q11.2DS
**Introduction**

22q11.2 deletion syndrome (22q11.2DS) is the most common recurrent microdeletion syndrome in humans, occurring in 1 in every 2,000-4,000 live births. In the majority of cases, a *de novo* 3 megabase (Mb) deletion occurs between the low copy repeats (LCRs) 22A-22D, resulting in the loss of 46 protein-coding genes.[1] 22q11.2DS has a highly variable phenotype, with characteristic features including congenital heart disease, palatal abnormalities, hypocalcaemia, mild-moderate intellectual disability and psychiatric disorders such as schizophrenia, attention deficit hyperactivity disorder (ADHD), anxiety disorder and autism spectrum disorder (ASD) [2-10].

People with 22q11.2DS are at an increased risk for both acute symptomatic and unprovoked epileptic seizures, although the reported rates are wide-ranging. Between 1% to 14.5% have hypocalcaemia-induced seizures.[11-14]. In adulthood, 17.6% of those exposed to psychotropic drugs have epileptic seizures, suggesting a reduced seizure threshold[12]. Between 3.8% and 36.8% have unprovoked seizures[8, 12-16]. Structural brain abnormalities in these individuals can include diffuse cerebral atrophy (18.8%), polymicrogyria (13.9%), hippocampal malrotation (10.9%), grey and white matter heterotopia (5.9%) and focal cortical dysplasia (2%)[17]. Between 1-8.3% of people with 22q11.2DS are diagnosed with genetic generalised epilepsy (GGE)[12-14, 17] and the deletion is also found in significant excess in GGE cohorts[18].

To date, studies investigating the prevalence of epileptic seizures and epilepsy in people with 22q11.2DS have relied on retrospective medical record review. Such records are less suited to systematic evaluation, because of differences between clinicians in diagnostic methods and documentation. This approach may furthermore miss cases of non-convulsive seizures not seen
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Clinically. Non-convulsive seizures usually have to occur several times before the affected individual and their family seek clinical advice[19]. Andrade et al. (2013) were the first to conduct a first-hand, systematic study of epilepsy in 22q11.2DS, including epileptologist, MRI and prolonged EEG assessment. They observed that 36.8% had epilepsy, although their sample consisted of only 19 adults[16]. Thus, previous research may have underestimated the prevalence of epileptic seizures and epilepsy in 22q11.2DS, particularly in young people. In addition, there is a dearth of research into salient characteristics of epileptic seizures in 22q11.2DS, such as seizure length and frequency, increases in which associate with poorer neurodevelopmental outcomes in the general population [20] [21].

Studies based primarily on historical medical record review have also assessed the relationships of epileptic seizures and epilepsy with cognitive and psychiatric development in 22q11.2DS. Neonatal seizures (mostly hypocalcaemia-induced) predict a more severe level of intellectual disability (ID) later in life[22]. Epilepsy is also associated with higher rates of developmental delay, but not with psychiatric disorder[15]. The associations of epilepsy with specific psychiatric diagnoses (e.g. ADHD) and other salient manifestations of 22q11.2DS, such as sleep disturbance [23] and motor coordination problems[3] have not been explored to date.

Our study had three aims:

First we explored the rates of an epilepsy diagnosis, seizures and seizure-like symptoms (behaviours which may reflect unrecognised epileptic seizures) in young people with 22q11.2DS and their unaffected control siblings, through data obtained from a validated questionnaire completed by the primary caregiver. To support these findings, we conducted a second stage of assessment with a sub-sample, involving interview, prolonged EEG assessment and medical record review. These data were then reviewed by an epileptologist, who made diagnoses of epileptic seizures and epilepsy.
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Secondly we sought to delineate salient characteristics of epileptic seizures in deletion carriers who took part in the second stage of assessment, such as aetiology, semiology, age of onset, length and frequency.

Thirdly we investigated whether epilepsy questionnaire responses were predicted by intellectual functioning (IQ and ID), psychopathology (diagnosis of ADHD, anxiety disorder and indicative ASD) motor coordination problems and sleep disturbance in deletion carriers.
Methods

Participants

We recruited 108 deletion carriers (57.4% male, mean age= 13.6 years, s.d.= 3.3 years, range = 6.2-20.5 years) and 60 of their unaffected control siblings (50% male, mean age= 13.1 years, s.d.= 3.2 years, range = 6.3-18.9 years) via UK genetics clinics and charities for chromosomal conditions. The deletion was identified in the clinics using standard methods (fluorescence in situ hybridisation or microarray) and confirmed in the MRC Centre for Neuropsychiatric Genetics and Genomics (microarray). The majority of deletion carriers had the typical de novo ~3Mb A-D deletion and all were haploinsufficient for TBX1, with the exception of one atypical B-D deletion (Table 1). We obtained informed written consent from primary caregivers and participants. The National Health Service Wales Research Ethics Committee approved our protocols.

Screening for lifetime history of epilepsy, seizures and seizure-like symptoms

We used the validated ‘Epilepsy Screening Questionnaire’ (ESQ, Table 2), developed by Ottman et al.(2010) [24] to screen for an epilepsy diagnosis (Item 9), seizures (Items 1 and 2,) and seizure-like symptoms (behaviours which may reflect unrecognised epileptic seizures, such as vacant episodes or uncontrolled body movements Items 3-8). We created two dichotomous summary variables: ‘any positive’: a positive response (‘yes’ or possibly’) to at least one item and ‘any positive excluding epilepsy’: a positive response to any of Item 1-Item 8 in those without epilepsy. The ESQ was originally self-report[24], however we asked the primary caregiver to complete it, given the ID in 22q11.2DS[2]. In the Ottman et al. (2010) validation study, participants were only asked about afebrile seizures and seizure-like symptoms if they didn’t have an epilepsy diagnosis[24], however we asked all items, to probe for additional unrecognised seizures in epilepsy patients.
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The ESQ was found to have high sensitivity for identifying epilepsy patients (96%) and a low false-positive rate amongst seizure-free individuals (7%). However, the estimated positive predictive value (PPV) in the general population was 23%[24], given the low rate of epilepsy(0.5-1%[25, 26]). The prevalence of epilepsy is higher in 22q11.2DS however (3.8-36.8%[8, 12-16]).

**Second stage of assessment of epileptic seizures and epilepsy**

To validate our findings from the ESQ, we conducted a second stage of assessment in a sub-sample of 40 deletion carriers and 4 controls reported with ‘any positive’ response to the ESQ.

A trained researcher interviewed the primary caregiver about ESQ-reported events (n = 37 deletion carriers, n = 4 controls), using an amended version of the validated semi-structured Seizure Classification Interview (SCI) developed by Ottman et al.[27, 28]. Diagnoses from the SCI show fair-excellent non-chance agreement with neurologist diagnoses. In the Ottman et al. (1990) validation study[27], seizures were classified in individuals with an epilepsy diagnosis.

We used the interview to help assess whether ESQ-reported events were epileptic seizures in all participants. We therefore combined the ‘grand mal’ and ‘small seizures’ sections into an ‘unusual spell’ section. We also added in a new section for febrile seizures and a supplementary section, conducted with children with capacity, which probed for auras and triggers (n= 16 deletion carriers, n = 4 control siblings). We undertook medical record reviews (n = 11 deletion carriers).

We conducted prolonged ambulatory electroencephalography (EEG) with 28 deletion carriers and 4 controls, with overnight video-monitoring (22q11.2DS: mean recording length = 13:41:16, s.d.= 04:59:40, range= 3:30:00-21:03:06, controls: mean = 11:14:38, s.d. = 05:14:36, range = 03:25:00- 14:25:23). Recordings were performed using a 64-channel Hydrocel
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Data from the second stage of assessment were reviewed by a consultant epileptologist who diagnosed and classified epileptic seizures and epilepsy according to International League Against Epilepsy (ILAE) criteria [29-31]. Both the epileptologist and a consultant neurophysiologist reviewed the EEG traces for background abnormalities and epileptiform discharges.

IQ and psychopathology

We derived the child’s full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ) scores from the Wechsler Abbreviated Scale of Intelligence (WASI)[32]. Intellectual disability (ID) was defined as FSIQ <70. We conducted the semi-structured Child and Adolescent Psychiatric Assessment interview (CAPA)[33] with the primary caregiver to diagnose ADHD and anxiety disorder, according to DSM-IV-TR [34] criteria. We screened for indicative ASD using the Social Communication Questionnaire. [35], completed by the primary caregiver.

Other neurodevelopmental problems

We screened for indicative developmental coordination disorder (DCD) using the Developmental Coordination Disorder Questionnaire (DCDQ)[36, 37], completed by the primary caregiver. Sleep disturbance was defined as a score of two on one item from the CAPA sleep section. Primary caregivers provided information on preterm birth and lifetime cardiovascular problems, recurrent infections and medication use.

Sample sizes for the ESQ, IQ, psychopathology and other neurodevelopmental problem datasets differ due to either the child or parent not completing part/all of one or more of the
Epilepsy and seizures in young people with 22q11.2 deletion syndrome measures. The primary caregiver was not available for the SCI interview for three deletion carriers who took part in EEG.

**Statistical analyses**

Statistical analyses were conducted in R version 3.5.1 ([https://www.R-project.org/](https://www.R-project.org/)).

**Screening for lifetime history of epilepsy, seizures and seizure-like symptoms**

We used logistic regressions to measure associations between deletion status (22q11.2DS/control) and the ‘any positive’ and ‘any positive excluding epilepsy’ ESQ-summary variables. Predictors were entered hierarchically, age first, then gender, then deletion status. We conducted a sensitivity analysis to explore whether lifetime history of psychotropic and/or anti-epileptic medication use, preterm birth and cardiovascular problems contributed to our findings. We investigated the relationship between deletion status and response to each ESQ item (positive/negative) using $\chi^2$/Fisher’s Exact Test. We conducted a logistic regression exploring whether a lifetime history of recurrent infections predicted febrile seizures in deletion carriers.

**Second stage of assessment of epileptic seizures and epilepsy**

For the ‘epilepsy diagnosis’ and ‘any positive excluding epilepsy’ ESQ variables, we calculated the percentage of deletion carriers who were diagnosed with epilepsy, epileptic seizures and febrile seizures by the epileptologist, respectively, as well as the rates of epileptiform discharges; no background abnormalities were observed. Given the high rate of ESQ-reported febrile seizures we observed in deletion carriers (24.1%), we repeated these analyses for this item. For controls, we repeated these analyses with the ‘any positive excluding epilepsy’ ESQ variable only (no controls were reported with epilepsy or febrile seizures, or had abnormal EEG findings).
We calculated the rate of different seizure aetiologies in deletion carriers diagnosed with epileptic seizures. We also explored characteristics of febrile and unprovoked seizures (the most common seizure aetiologies in our sample) such as the semiology (rates of generalised and focal) median age of onset (months), the median number, the median length (seconds) and response rates to different frequency categories (e.g. less than once a month). No controls were diagnosed with epileptic seizures.

**Association of the ESQ with neurodevelopmental problems in 22q11.2DS**

In young people with 22q11.2DS, we used logistic regressions to explore the associations of the ‘any positive’ ‘any positive excluding epilepsy’ and ‘febrile seizure’ variables with IQ scores, ID, psychopathology, indicative DCD and sleep disturbance. Predictors were entered hierarchically, age first, then gender and finally the neurodevelopmental variable. We compared FSIQ, VIQ and PIQ scores and rates of ID, psychopathology, indicative DCD and sleep disturbance between deletion carriers and controls using t-tests and χ² tests.

**Results**

Table 1 displays descriptive statistics about our sample
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### Table 1. Descriptive statistics about our sample

<table>
<thead>
<tr>
<th>Deletion aetiology</th>
<th>De Novo 77.8%</th>
<th>Inherited 8.3%</th>
<th>Unknown 13.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion type</td>
<td>~3Mb A-D 75.9%</td>
<td>~2Mb A-C 0.9%</td>
<td>~1.5Mb A-B 6.5%</td>
</tr>
<tr>
<td></td>
<td>Atypical B-D 0.9%</td>
<td>Unknown 15.8%</td>
<td></td>
</tr>
<tr>
<td>Family Ethnic Background</td>
<td>European 85.2%</td>
<td>Mixed 10.2%</td>
<td>Non-European 1.9%</td>
</tr>
<tr>
<td></td>
<td>Unknown 2.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest Parental Qualification*</td>
<td>Low (O-Levels/GCSEs) 23.1%</td>
<td>Middle (A-Leaves/highers/vocational Training) 32.4%</td>
<td>High (university degree and/or other higher postgraduate qualification) 32.4%</td>
</tr>
<tr>
<td></td>
<td>Unknown 12.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Income</td>
<td>≤ £19,999 22.2%</td>
<td>£20,000 - £39,999 24.1%</td>
<td>£40,000 - £59,999 21.3%</td>
</tr>
<tr>
<td></td>
<td>≥ £60,000 23.1%</td>
<td>Unknown 9.3%</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean 13.6</td>
<td>SD 3.3</td>
<td>Range 6.2-20.5</td>
</tr>
<tr>
<td>22q11.2DS</td>
<td>Controls 13.1</td>
<td>Mean 3.2</td>
<td>Range 6.3-18.9</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (%)</td>
<td>Female (%)</td>
<td></td>
</tr>
<tr>
<td>22q11.2DS</td>
<td>62 (57.4)</td>
<td>46 (42.6)</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>30 (50)</td>
<td>30 (50)</td>
<td></td>
</tr>
</tbody>
</table>
Epilepsy, seizures and seizure-like symptoms in 22q11.2DS and control siblings

Table 2 shows the rates of positive responses on each ESQ item. 63.9% (69/108) of deletion carriers had ‘any positive’ response compared to 13.3% (8/60) of controls \((b=2.49, z=5.67, \text{OR}=12, p<0.001)\). 11.1% of deletion carriers had an epilepsy diagnosis, yet when excluding these cases 59.4% (57/96) of deletion carriers had ‘any positive excluding epilepsy’ compared to 13.3% (8/60) of controls \((b=2.27, z=5.15, \text{OR}=9.66, p<0.001)\). Around a quarter of deletion carriers had febrile seizures (controls 0%, \(p<0.001\), Table 2). Rates of four of the seizure-like symptom items were higher in cases than controls (Table 2). Age and gender did not influence these relationships.
Table 2. Rates of positive responses on each item of the Epilepsy Screen Questionnaire in young people with 22q11.2DS and their unaffected control siblings

<table>
<thead>
<tr>
<th>Item</th>
<th>Positive response</th>
<th>( \chi^2 )</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did your son/daughter ever have a seizure or convulsion caused by a high fever?</td>
<td>26 (24.3) 0 (0)</td>
<td>17</td>
<td>17.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. Other than the seizures associated with high fevers, has your son/daughter ever had a seizure, convulsion, fit, or spell - under any circumstances?</td>
<td>26 (24.1) 0 (0)</td>
<td>16.8</td>
<td>16.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3. Other than the seizures associated with high fevers, has your son/daughter ever had uncontrolled movements of part or all of his/her body such as twitching, jerking, shaking or going limp?</td>
<td>21 (19.8) 2 (3.3)</td>
<td>8.72</td>
<td>7.1</td>
<td>0.003</td>
</tr>
<tr>
<td>4. Other than the seizures associated with high fevers, has your son/daughter ever had an unexplained change in his mental state or level of awareness; or an episode of ‘spacing out’ that he/she could not control?</td>
<td>19 (17.8) 1 (1.7)</td>
<td>9.44</td>
<td>12.6</td>
<td>0.002</td>
</tr>
<tr>
<td>5. Does your son/daughter daydream or stare into space more than other children?</td>
<td>43 (40.2) 5 (8.3)</td>
<td>19</td>
<td>7.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6. Have you ever noticed him/her to have any unusual body movements when exposed to strobe lights, video games, flickering lights, or sun glare?</td>
<td>3 (2.8) 0 (0)</td>
<td>Fisher’s Exact Test</td>
<td>–</td>
<td>0.553</td>
</tr>
<tr>
<td>7. Shortly after waking up, either in the morning or after a nap, have you ever noticed your son/daughter have uncontrollable jerking or clumsiness, such as dropping things or things suddenly flying from his/her hands?</td>
<td>10 (9.3) 0 (0)</td>
<td>Fisher’s Exact Test</td>
<td>–</td>
<td>0.014</td>
</tr>
<tr>
<td>8. Has your son/daughter ever had any other type of repeated unusual spells?</td>
<td>7 (6.5) 0 (0)</td>
<td>Fisher’s Exact Test</td>
<td>–</td>
<td>0.051</td>
</tr>
<tr>
<td>9. Has your son/daughter ever been diagnosed with a seizure disorder or epilepsy?</td>
<td>12 (11.1) 0 (0)</td>
<td>Fisher’s Exact Test</td>
<td>–</td>
<td>0.004</td>
</tr>
</tbody>
</table>
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17.6% (19/108) had a lifetime history of psychotropic and/or antiepileptic medication use. 13.6% (14/103) of deletion carriers and 4.3% (2/46) of controls were born prematurely. 64.8% (68/105) of deletion carriers and 1.7% (1/59) of controls had cardiovascular problems. These comorbidities did not influence the association of deletion status with ‘any positive’

The majority of deletion carriers had a lifetime history of recurrent infections (68.9%, 73/106, controls 10.9%, 6/55, p<0.001). Deletion carriers with recurrent infections were not more likely to report febrile seizures however (b=0.78, z=1.41, p=0.157).

**Second stage of assessment of epileptic seizures and epilepsy**

Deletion carriers who took part in the second stage of assessment were older (mean age=14.6) than those that didn’t (mean age= 12.4, p<0.001). Control siblings who took part had a higher FSIQ (114) than those that didn’t (106, p =0.041).

The results from the second stage of assessment are shown in Table 3. The vast majority of deletion carriers reported as having an epilepsy diagnosis, who were subsequently interviewed, had their diagnosis confirmed by our epileptologist (5/6, 83%). The remaining individual had an isolated neonatal unprovoked generalised tonic-clonic seizure (GTCS).

Just over half of the deletion carriers reporting ‘any positive excluding epilepsy’, who were interviewed, were subsequently diagnosed with epileptic seizures (16/31) by our epileptologist. In two, the diagnosis was ‘possible’ non-motor absence seizures (based on a history of daydreaming spells). Medical records were not available in these two cases, but their caregivers reported they had not seen a clinician for these events. Interestingly, during the EEG assessment one displayed short bursts of generalised and left hemisphere spike-and-slow-wave discharges, occurring during sleep and shortly after awakening. Two of the 16 individuals diagnosed with epileptic seizures also met criteria for an epilepsy diagnosis. The primary
caregiver for one described a history of repeated unprovoked GTCS in the SCI, but reported the child had not been diagnosed with epilepsy. However, a child development clinic letter listed epilepsy as a diagnosis. The other individual was diagnosed with epilepsy based on a history of repeated ‘staring spells’ described in the SCI, classified as non-motor absence seizures by our epileptologist. Medical records were unavailable, but the primary caregiver reported that a paediatrician had described these events as ‘possible absence seizures’ and that further assessments were not conducted as these events had stopped. Interestingly, this child showed brief generalised spike-and-slow-wave epileptiform discharges shortly after awakening. The remaining deletion carriers (15/31) were diagnosed with non-epileptic events (e.g. daydreaming), although one showed brief generalised, left and right hemisphere spike-and-slow-wave discharges during sleep. Eighty percent of these individuals (12/15) were only reported with seizure-like symptoms on the ESQ.

The vast majority of deletion carriers with ESQ-reported febrile seizures, who were interviewed, were diagnosed with febrile seizures by the epileptologist (16/17, 94%). The remaining individual was diagnosed with fever-related delirium/drowsiness. In control siblings, all individuals reported as having ‘any positive excluding epilepsy’, who were interviewed, were diagnosed with non-epileptic events.
Table 3. Results from the second stage of assessment in young people with 22q11.2DS and control siblings

<table>
<thead>
<tr>
<th>ESQ variable</th>
<th>22q11.2DS</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n screening positive/total n (%)</td>
<td>Interview completed?</td>
<td>Diagnosis confirmed by epileptologist? (%)</td>
<td>EEG completed? (%)</td>
<td>Epileptiform discharges? (%)</td>
</tr>
<tr>
<td>ESQ: epilepsy diagnosis</td>
<td>12/108 (11)</td>
<td>6/12 (50)</td>
<td>5/6 (83)</td>
<td>2/12 (17)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ESQ: 'any positive excluding epilepsy'</td>
<td>57/96 (59)</td>
<td>31/57 (54)</td>
<td>16/31 (52)</td>
<td>26/57 (46)</td>
<td>3/26 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESQ variable</th>
<th>Control siblings</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n screening positive/total n (%)</td>
<td>Interview completed?</td>
<td>Diagnosis confirmed by epileptologist? (%)</td>
<td>EEG completed? (%)</td>
<td>Epileptiform discharges? (%)</td>
</tr>
<tr>
<td>ESQ: 'any positive excluding epilepsy'</td>
<td>8/60 (13)</td>
<td>4/8 (50)</td>
<td>0/4 (0)</td>
<td>4/8 (50)</td>
<td>0/4 (0)</td>
</tr>
</tbody>
</table>

ESQ, Epilepsy Screen Questionnaire, EEG, electroencephalography.
Table 4 shows salient characteristics of epileptic seizures in deletion carriers. Febrile and unprovoked epileptic seizures were the most common seizure aetiologies (77.3% and 45.5%, respectively). All febrile seizures were convulsive, with a median estimated length of 2.5 minutes. On average febrile seizures began within the first two years of life and were recurrent (one child experienced seven). Unprovoked seizures were not linked to a structural aetiology in 60% of deletion carriers. In the remaining 40%, unprovoked seizures were seen in people with structural brain abnormalities or potential acquired causes; right hemisphere polymicrogyria, perinatal subdural haematoma, possible post pneumococcal meningitis (information obtained from the SCI only) and neonatal hypoxic-ischaemic encephalopathy (information obtained from the SCI and medical records). Unprovoked seizures were mostly generalised, on average lasting for ~2 minutes and had a median age of onset within the first three years of life. At their most frequent, unprovoked seizures occurred one-to-four times a month in the majority. However, 30% experienced unprovoked seizures on at least a daily basis. These three individuals were had: focal motor seizures with post-ictal left-sided numbness upon awakening; ‘possible’ absence seizures and; GTCS with non-motor absences.

Other seizure aetiologies not shown in Table 4 include hypocalcaemia (9.1%, 2/22, GTCS in both cases), cardiac surgery (4.5%, 1/22, focal motor seizure) and hypoxic-ischaemic encephalopathy (4.5%, 1/22, focal motor seizure, possibly to bilateral tonic-clonic).
Table 4. Rates and characteristics of febrile and unprovoked seizures in young people with 22q11.2DS who took part in the second stage of assessment

<table>
<thead>
<tr>
<th>Seizure aetiology</th>
<th></th>
<th>n/ n with epileptic seizures (%)</th>
<th>Seizure semiology (%)</th>
<th>Mean age of onset in months (range)a</th>
<th>Median seizure length in secondsb</th>
<th>Median number of seizures</th>
<th>Frequency (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile</td>
<td></td>
<td>17/22 (77)</td>
<td>Generalised</td>
<td>17 (100)</td>
<td>14 (0-168)</td>
<td>150 (10-900)</td>
<td>2 (1-7)</td>
</tr>
<tr>
<td></td>
<td>Unprovoked</td>
<td>10/22 (46)</td>
<td>8/10 (80)</td>
<td>2/10 (20)</td>
<td>33.0 (0-108)</td>
<td>135 (3-330)</td>
<td>3 (30)</td>
</tr>
<tr>
<td></td>
<td>Genetic</td>
<td>6/22 (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structural</td>
<td>4/22 (18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a For deletion carriers with multiple types of unprovoked seizure, the earliest age when seizures appeared was used. Within the range, '0' refers to deletion carriers who had their first seizure during the first month of life.

b For deletion carriers with seizures of differing lengths, the time of the longest seizure was used.

c Primary caregivers were asked to indicate how often seizures occurred in their child, when they were at their most frequent.
Association of the ESQ with neurodevelopmental problems in 22q11.2DS

IQ and ID

The mean FSIQ, PIQ and VIQ of deletion carriers were significantly lower than controls (Supplementary Table 1). One deletion carrier had a higher-than-average FSIQ (117). Twelve percent (12/99) had an average FSIQ (86-115) and 40.4% (40/99) had a FSIQ in the borderline range (71-85). Around forty-one percent (41/99) had mild ID (55-70) and 5.1% (5/99) had moderate ID (IQ<55). By contrast, 94.5% (52/55) of control siblings had an average, or higher-than-average FSIQ and only three (5.5%) had a borderline FSIQ. ‘Any positive’ was more common in deletion carriers with a lower PIQ (p=0.018, Table 5). This relationship was not observed for ‘any positive excluding epilepsy’ (p=0.060) or febrile seizures (p=0.105). None of the ESQ variables were predicted by FSIQ, VIQ or ID. Age and gender did not contribute to our findings.

Psychopathology, sleep disturbance and motor coordination problems

We found higher rates of psychopathology, sleep disturbance and indicative DCD in deletion carriers relative to controls (Supplementary Table 1). Deletion carriers with ADHD were around three times more likely to have ‘any positive’ and those with indicative ASD and DCD were around four times more likely (Table 5). The associations with indicative ASD and DCD held for ‘any positive excluding epilepsy’ (p=0.018 and p=0.026, respectively), although the relationship with ADHD disappeared (p=0.163). None of these relationships remained for febrile seizures. None of the ESQ variables were predicted by psychiatric disorders as a group, anxiety disorder or sleep disturbance. Age and gender did not contribute to our findings.
Supplementary Table 1. IQ scores and rates of neurodevelopmental problems in young people with 22q11.2 deletion syndrome and control siblings.

<table>
<thead>
<tr>
<th>Measure</th>
<th>22q11.2 DS</th>
<th>Control siblings</th>
<th>t</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>99</td>
<td>72.05 ± 12.29</td>
<td>55</td>
<td>108.58 ± 15.3</td>
<td>15.19</td>
</tr>
<tr>
<td>PIQ</td>
<td>99</td>
<td>75.24 ± 12.83</td>
<td>55</td>
<td>109.29 ± 16.62</td>
<td>13.17</td>
</tr>
<tr>
<td>VIQ</td>
<td>100</td>
<td>73.13 ± 12.67</td>
<td>55</td>
<td>106.45 ± 14.77</td>
<td>14.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurodevelopmental problem</th>
<th>Total</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Total</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>( \chi^2 )</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID</td>
<td>99</td>
<td>42 (42.4)</td>
<td>57 (57.6)</td>
<td>55</td>
<td>0(0)</td>
<td>55 (100)</td>
<td>32.08</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>108</td>
<td>53 (49.1)</td>
<td>55 (50.9)</td>
<td>53</td>
<td>2 (3.8)</td>
<td>51 (96.2)</td>
<td>32.44</td>
<td>24.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD</td>
<td>106</td>
<td>30 (28.3)</td>
<td>76 (71.7)</td>
<td>47</td>
<td>1 (2.1)</td>
<td>46 (97.9)</td>
<td>13.81</td>
<td>17.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>108</td>
<td>31 (28.7)</td>
<td>77 (71.3)</td>
<td>49</td>
<td>2 (4.1)</td>
<td>47 (95.9)</td>
<td>12.3</td>
<td>9.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any sleep problem</td>
<td>107</td>
<td>63 (58.9)</td>
<td>44 (41.1)</td>
<td>50</td>
<td>10 (20)</td>
<td>40 (80)</td>
<td>20.7</td>
<td>5.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indicative ASD</td>
<td>90</td>
<td>37 (41.1)</td>
<td>53 (58.9)</td>
<td>48</td>
<td>0 (0)</td>
<td>48 (100)</td>
<td>26.96</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indicative DCD</td>
<td>95</td>
<td>79 (83.2)</td>
<td>16 (16.8)</td>
<td>54</td>
<td>3 (5.6)</td>
<td>51 (94.4)</td>
<td>83.78</td>
<td>79.88</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FSIQ, full-scale IQ, PIQ, performance IQ, VIQ, verbal IQ, ID, intellectual disability, ADHD, attention deficit hyperactivity disorder, ASD, autism spectrum disorder, DCD, developmental coordination disorder.
Table 5. IQ scores and rates of neurodevelopmental problems for young people with 22q11.2DS on the ‘any positive’ summary variable.

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Any positive</th>
<th>b</th>
<th>z</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (s.d.)</td>
<td></td>
<td></td>
<td>Yes (s.d.)</td>
<td></td>
</tr>
<tr>
<td>Full-scale</td>
<td>99</td>
<td>73.94 (13.31)</td>
<td>-0.02</td>
<td>-1.39</td>
<td>0.98</td>
<td>0.163</td>
</tr>
<tr>
<td>Performance</td>
<td>99</td>
<td>70.35 (11.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>100</td>
<td>78.49 (14.05)</td>
<td>-0.04</td>
<td>-2.36</td>
<td>0.96</td>
<td>0.018</td>
</tr>
<tr>
<td>Verbal</td>
<td>100</td>
<td>72.31 (10.94)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurodevelopmental problem</th>
<th>n affected/total n</th>
<th>Any positive</th>
<th>b</th>
<th>z</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (%)</td>
<td></td>
<td></td>
<td>Yes (%)</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>42 / 99</td>
<td>17 (36.2)</td>
<td>0.44</td>
<td>1.02</td>
<td>1.55</td>
<td>0.921</td>
</tr>
<tr>
<td>Any psychiatric disorder</td>
<td>53 / 108</td>
<td>33 (56.9)</td>
<td>0.76</td>
<td>1.87</td>
<td>2.13</td>
<td>0.062</td>
</tr>
<tr>
<td>ADHD</td>
<td>30 / 106</td>
<td>10 (20)</td>
<td>1.19</td>
<td>2.32</td>
<td>3.28</td>
<td>0.021</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>31 / 108</td>
<td>11 (22.0)</td>
<td>0.6</td>
<td>1.36</td>
<td>1.83</td>
<td>0.175</td>
</tr>
<tr>
<td>Any sleep problem</td>
<td>63 / 107</td>
<td>31 (62)</td>
<td>-0.24</td>
<td>-0.59</td>
<td>0.79</td>
<td>0.558</td>
</tr>
<tr>
<td>Indicative ASD</td>
<td>37 / 90</td>
<td>11 (25.6)</td>
<td>1.35</td>
<td>2.86</td>
<td>3.86</td>
<td>0.004</td>
</tr>
<tr>
<td>Indicative DCD</td>
<td>79 / 95</td>
<td>33 (73.3)</td>
<td>1.52</td>
<td>2.31</td>
<td>4.56</td>
<td>0.021</td>
</tr>
</tbody>
</table>

FSIQ, full-scale IQ, PIQ, performance IQ, VIQ, verbal IQ, ID, intellectual disability, ADHD, attention deficit hyperactivity disorder, ASD, autism spectrum disorder, DCD, developmental coordination disorder
Comorbidity of ‘any positive’ indicative DCD, ADHD and indicative ASD was common in 22q11.2DS (Figure 1). 58.2% (46/79) with indicative DCD had ‘any positive’, as did 70.3% (26/37) of those with indicative ASD and 66.7% (20/30) of those with ADHD. 10.6% (10/94) had ‘any positive’, indicative DCD, ADHD and indicative ASD.

Figure 1. The overlap of ‘any positive’ on the Epilepsy Screen Questionnaire, indicative DCD, ADHD and indicative ASD in 22q11.2DS. DCD, developmental coordination disorder, ADHD, attention-deficit hyperactivity disorder, ASD, autism spectrum disorder.

Discussion

We showed that 11.1% of deletion carriers screened positive for an epilepsy diagnosis, but over half were reported with seizures or seizure-like symptoms without a diagnosis. In addition, 24.1% were reported with febrile seizures. Results from a second stage of assessment (interview, prolonged ambulatory EEG, medical records, epileptologist review) suggested our rates of questionnaire-reported epilepsy and febrile seizures were accurate, and highlighted that epilepsy and epileptic seizures may be missed during routine clinical care in some deletion carriers. Cases who screened positive on the epilepsy questionnaire had higher rates of ADHD,
indicative ASD and DCD, and lower PIQ scores. These associations remained when cases with an epilepsy diagnosis were excluded, with the exception of ADHD, and none held for febrile seizures. We propose that risk for epileptic seizures in deletion carriers may be symptomatic of underlying aberrant synaptic plasticity and an imbalance in neuronal excitation-inhibition, that also gives rise to impaired cognition, psychopathology and motor coordination problems.

**Epilepsy, seizures and seizure-like symptoms in young people with 22q11.2DS**

We observed a ~60% rate of ESQ-reported seizures and seizure like-symptoms in deletion carriers, after excluding cases with reported epilepsy. These events were more prevalent than in controls and showed many of the same associations with poorer neurodevelopmental outcomes that an epilepsy diagnosis carries. Results from our second stage of assessment suggested that half of deletion carriers reported with these events had ‘true’ epileptic seizures, mainly febrile and/or unprovoked. Crucially, this assessment also suggested that non-convulsive seizures, interictal epileptiform discharges, and epilepsy may be missed during routine clinical care in some deletion carriers. These findings are limited by the ‘possible’ seizure in some deletion carriers, likely caused by the remote epileptologist assessment. The ESQ also may not detect some deletion carriers with clinically diagnosed epilepsy, given that this occurred in one case when cross-referencing with medical records. Ultimately, systematic study of all ESQ-reported seizures and seizure-like symptoms, incorporating direct epileptologist assessment, will better address whether epilepsy is underdiagnosed in 22q11.2DS.

*Febrile seizures*
Epilepsy and seizures in young people with 22q11.2 deletion syndrome

Our rate of reported febrile seizures in deletion carriers (24.1%) is higher than previous estimates (2-6%) [11, 12, 14]. This suggests a reduced seizure threshold, supporting previous findings in adult deletion carriers with psychotropic and hypocalcaemia-induced seizures. [12]. Alternatively, the high rate may be due to frequent infections in this syndrome (68.9% in our study). However, we did not observe an association between recurrent infections and febrile seizures.

Febrile seizures were ‘simple’, the subtype considered to be relatively benign[38]. Supporting this, ESQ-reported febrile seizures did not associate with poorer neurodevelopmental outcomes. Future longitudinal studies may better characterise the relationship of febrile seizures with neurodevelopmental trajectories in 22q11.2DS.

Unprovoked seizures

The median age of onset of unprovoked seizures (33 months) and febrile seizures (14 months) suggests that deletion carriers are at risk for epileptic seizures from early in life. Unprovoked seizures were occurring once a day or more when at their most frequent in 30% of deletion carriers.

Association of the ESQ with neurodevelopmental problems in 22q11.2DS

The associations of ESQ-reported epilepsy, seizures and seizure-like symptoms with impaired cognition, psychopathology and motor coordination problems in deletion carriers replicate findings from the general population[26, 41, 42] and suggest shared neurobiological risk pathways. One pathway could be aberrant synaptic plasticity. This associates with epileptic seizures and ASD-related behaviours via an imbalance in neuronal excitation-inhibition[43]. In a mouse model of ASD, aberrant synaptic plasticity linked with motor coordination and learning deficits via impaired cerebellar long-term depression response and synaptic pruning [44]. Synaptic plasticity is important in executive function development during adolescence, a
Epilepsy and seizures in young people with 22q11.2 deletion syndrome

behavioural impairment in ADHD[45]. Aberrant synaptic plasticity also shows links with impaired cognition[46] and the emergence of the sensory, cognitive, motor and psychotic features that characterise schizophrenia[47], for which 22q11.2DS confers risk (22%)[6]. Hemizygosity for DGCR8 and ZDHHC8 in 22q11.2DS results in altered microRNA processing and altered protein palmitoylation, respectively, that may lead to aberrant synaptic plasticity. Subtle changes in neuronal circuitry are observed in mouse models of 22q11.2DS, such as reduced dendritic branching[48].

Epileptic seizures may also cause neurobiological changes resulting in impaired cognition and ASD-related behaviours[43] and may alter cerebral functional organisation of motor control [49]. Paroxysmal epileptic activity associates with poorer performance on attention tests[50]. Early-life seizures may therefore have deleterious effects on a vulnerable neural network in 22q11.2DS, exacerbating impaired cognition, ADHD and ASD-symptoms and motor coordination problems. Future longitudinal designs are warranted to assess this hypothesis.

Limitations of the Epilepsy Screen Questionnaire, and implications for our findings

The PPV of the ESQ is low in the general population (23%), however, the higher prevalence of epilepsy in 22q11.2DS would increase the PPV of the questionnaire. We predict that a minority of deletion carriers who screened positive may not true have epileptic seizures. The results of our second-stage of assessment show that the vast majority of ESQ-reported epilepsy diagnoses were genuine, and half of deletion carriers reported with seizures or seizure-like symptoms have ‘true’ epileptic seizures. Future studies replicating our method should ensure all individuals with ‘any positive’ take part in the second stage to establish the PPV of the ESQ for epileptic seizures in 22q11.2DS.
Clinical implications

Our work reinforces that not only are children with 22q11.2DS at risk of acute symptomatic seizures and epilepsy during the early years of life, but that epilepsy could be underdiagnosed. We recommend a high-index of suspicion for epileptic seizures in 22q11.2DS, with epileptologist consultation and video-EEG for uncertain cases. Early intervention for epileptic seizures is particularly important given the associations with poorer neurodevelopmental outcomes. A micro-chromosomal array should be considered to screen for 22q11.2DS in children presenting with epileptic seizures and congenital heart disease, palatal abnormalities, hypocalcaemia, ID psychopathology or motor deficits.

In conclusion, we demonstrated that ~60% of young people with 22q11.2DS screen for seizures and seizure-like symptoms in the absence of an epilepsy diagnosis. Systematic investigation of a sub-sample show that epileptic seizures may be missed during routine clinical care and that epilepsy may be underdiagnosed. Risk for epileptic seizures in 22q11.2DS may be symptomatic of aberrant synaptic plasticity and an imbalance in neuronal excitation-inhibition, which also leads to cognitive impairment, psychopathology and motor coordination problems. We observed a high rate of febrile seizures (24.1%), which provides further evidence for a reduced seizure threshold in 22q11.2DS. Highlighting the prevalence of epileptic seizures and epilepsy and their relationship with neurodevelopment in 22q11.2DS could allow focused intervention by clinicians, ultimately improving outcomes in young people with this syndrome.

Acknowledgements

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Epilepsy and seizures in young people with 22q11.2 deletion syndrome

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**Disclosure**

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References

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