Retroviral case-note review in a tertiary paediatric neurology unit. For all 27 children seen with a definite diagnosis of AES between 1972 and 2002, a review of clinical histories, videotapes, and EEG/ECG studies was undertaken. Main outcome measures were: age of onset, frequency and type of syncopes; age of onset and frequency of AES; type and duration of induced epileptic seizures; effect of treatment of syncopal and epileptic components.

Results: Median age of onset of syncopes was 8 months (range 0.2–120), frequency 2 in total to 40/day, median total 17 months (range 7–120), frequency from total 1 to 3/day, median total 3. The epileptic component was almost always bilateral clonic; three had additional epilepsy, one each with complex partial seizures, myoclonic absences, and febrile seizures plus. Median duration of epileptic component was 5 minutes (range 0.5–40, mean 11). Cardiac pacing prevented RAS in two patients: most other anti-syncope therapies were ineffective. Diazepam terminated the epileptic component in 6/8. Valproate or carbamazepine abolished AES in 5/7 without influencing syncope frequency. Conclusions: Although uncommon compared with simple syncopes, syncope triggered epileptic seizures (AES) are an important treatable basis of status epilepticus.

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METHODS
Setting
The Fraser of Allander Neurosciences Unit is a tertiary referral unit for paediatric neurology which serves the West of Scotland (population 3 million) but may take referrals from elsewhere. Since its opening in 1972 a diagnostic index has been maintained of all patients seen.

Information retrieval
The diagnostic index was searched for the coded diagnosis of AES from 1972 until the end of 2002. All case records were reviewed in detail by the authors. All available home or hospital video recordings were reviewed as well as EEG and ECG traces. The coded diagnosis of AES was only accepted if both the history of syncope and of the triggered epileptic seizure was convincing to all authors. Box 1 shows the levels of evidence we used for establishing the epileptic component. Case histories, EEG/ECG records, and/or video recordings of 14 of the children were already in the literature,1 2 11 13–15 and these publications were reviewed.

RESULTS
Patient demographics
A total of 27 children had a convincing history of AES, with the first patient being recognised in 1978 and the next two in 1982. Of this total of 27, 21 were referred from the West of Scotland, 1 from Northeast Scotland, 3 from England, 1 from Wales, and 1 from the USA. All patients were seen at one time by the corresponding author (JBPS). There were 11 boys and 16 girls.

Age of onset and frequency of syncopes
The age of onset of syncopes ranged from 5 days (0.2 months) to 10 years (120 months) with a median of 8 months.

The frequency of syncopes varied from 2 in total to 40/day. The median was of the order of 200 syncopes, but since 11 of the children had a history of daily syncopes, the figures for total number of syncopes were in the main approximations.

Type of syncopes
We grouped the syncopes into five types on the basis of clinical description, aided when possible by the appearances of recorded events.
REFLEX ANOXIC SEIZURES/REFLEX ASYSTOLIC SYNCOPE (RAS)
There were 9 children whose syncopes were judged to be of this nature, with a typical history of short latency onset syncopes most often precipitated by unexpected hurt. Of these, 7 had ECG recordings during ocular compression (5 children), on head-up tilt (1 child), or on cardiac monitoring at home (1 child). Median cardiac asystole was 28 seconds (range 17–31).

PROLONGED EXPIRATORY APOnea/CYANOTIC BREATH-HOLDING SPELLS
In 6 children the clinical description was of “blue breath-holding” or cyanotic breath-holding spells, otherwise called prolonged expiratory apnoea, with expiratory grunting apnoea and deep cyanosis in response to frustration. When syncopes occurred during monitoring (3 children), prolonged cardiac asystole was not seen.

INFANTILE SYNCOPES OF UNCERTAIN OR MIXED ORIGIN
In 9 children either we could not decide which of the above mechanisms was operative or else there was evidence of a mixed mechanism. In the most dramatic example there was simultaneous prolonged expiratory grunting and prolonged asystole (23–24 seconds).

VasoVagal Syncope
Two children had more typical vasoVagal syncope, 1 while having her pierced ears cleaned, and 1 (aged 10 years) during hair grooming.

Compulsive Valsalva manoeuvres
One boy with autistic spectrum disorder had very frequent daily compulsive Valsalva manoeuvres.

ANoxic-epileptic seizures: age of onset and frequency
The median age of onset of AES was 17 months (range 7–120). The frequency varied from a total of just one to 3/day, the median being 3 AES in total.

Type of epileptic component of AES
In almost all children the epileptic component could be described as bilateral clonic. Sometimes there was horizontal eye deviation or rhythmically interrupted vocalisation. In one child, what appeared to be absence status followed the clonic epileptic component. In 3 children there were in addition unprovoked epileptic seizures, that is epilepsy, the syncope triggered epileptic seizures being reportedly identical to the spontaneous episodes. There was one example each of myoclonic absences, generalised epilepsy with febrile seizures—clonic epileptic seizures with and without fever—and temporal lobe complex partial seizures.

Duration of epileptic component of AES
The duration of the syncope triggered epileptic seizures varied from 28 seconds (Stephenson, case 11.2) to 40 minutes (mean 11 minutes, median 5 minutes). In about half (12 children) the epileptic component lasted for 10 minutes or more, and in 4 children for 30 minutes or more. The epileptic component was witnessed by medical staff in 16 children, and in these the duration of the epileptic component was 10 minutes or more in 8 and 30 minutes or more in 4.

TREATMENT OF THE SYNCOPAL COMPONENT OF AES
Most medications, including iron supplements and piracetam were unhelpful. In one child with RAS, atropine was associated with improvement, and in another was ineffective. In the autistic boy with compulsive Valsalva manoeuvres, naltrexone had at least temporary benefit. Permanent cardiac pacing prevented RAS, and therefore AES in 2 severely affected children. In one child with very frequent AES from “breath-holding” prolonged expiratory apnoea, psychological methods led to no benefit.

ACUTE TREATMENT OF THE EPILEPTIC COMPONENT OF AES
Rectal or intravenous diazepam was given by emergency doctors in 7 children and was effective in 6, albeit one child required two injections. In the diazepam non-responder, intravenous phenobarbitone and rectal paraldehyde were required in the intensive care unit, and this child later had cardiac pacing. In addition, the child with compulsive Valsalvas was given diazepam at home without evident benefit.

PROPHYLACTIC TREATMENT OF THE EPILEPTIC COMPONENT OF AES
Sodium valproate or carbamazepine was effective in 5 of 7 children to whom it was given. By effective we mean that the epileptic component of the AES was abolished, but the syncopes continued unchanged.

FREQUENCY OF AES COMPARED WITH FREQUENCY OF SYNCOPe
Except in a few instances, there were in any child vastly more syncopes, that is pure anoxic seizures, than there were AES. In 3 children in whom a more precise ratio could be calculated, about 7–8% of syncopes developed into AES. These results are summarised in table 1.
Table 1  Clinical data on 27 children with a history of AES

<table>
<thead>
<tr>
<th>Case no./sex/from</th>
<th>Ref./case</th>
<th>Syncope onset (mth)</th>
<th>Syncope type/frequency</th>
<th>AES onset (mth)</th>
<th>Epileptic component/ duration (min)</th>
<th>Evidence of epileptic component</th>
<th>AES total</th>
<th>Therapy (bold type = effective)</th>
<th>Other epileptic seizures</th>
<th>Other details/FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M 11</td>
<td></td>
<td>6–7 RAS 3/day</td>
<td></td>
<td>15 Clonic</td>
<td>1 3</td>
<td>–</td>
<td>–</td>
<td>OC 22s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 M 11</td>
<td></td>
<td>9 RAS Several</td>
<td></td>
<td>11 Clonic</td>
<td>1 2</td>
<td>–</td>
<td>–</td>
<td>OC 30 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 F 11</td>
<td></td>
<td>15 RAS 1/month BHS 3/day</td>
<td></td>
<td>48 Clonic</td>
<td>Focal 1 1+</td>
<td>Carbamazepine</td>
<td>Same</td>
<td>OC 17 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 M 5 U 11</td>
<td></td>
<td>0.5 RAS 3/week CVM Daily</td>
<td></td>
<td>7 Clonic</td>
<td>Myoclonic absence 2c  Many</td>
<td>Clonazepam</td>
<td>Same</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 M 3 U 11</td>
<td></td>
<td>30 CVM Daily</td>
<td></td>
<td>30 Clonic (vibratory) 1/2</td>
<td>2a Many</td>
<td>Wrestler’s belt</td>
<td>Diazepam</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 M 4</td>
<td></td>
<td>5 PEA Daily</td>
<td></td>
<td>10 Clonic</td>
<td>2b Many</td>
<td>Paraldehyde Psychology</td>
<td>–</td>
<td>Brother PEA &amp; FS up to 20 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 F 11</td>
<td></td>
<td>30 VVS 84 Clonic</td>
<td></td>
<td>4b 1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Ear piercing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 F 6</td>
<td></td>
<td>6 RAS 18 Clonic</td>
<td></td>
<td>4a 10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>CM 31 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 F 1</td>
<td></td>
<td>8.1 PEA 5 Clonic</td>
<td></td>
<td>3 20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>OC 5 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 F 11</td>
<td></td>
<td>6 BHS 20 Clonic</td>
<td></td>
<td>4a 3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>OC 12 s</td>
<td>One AES febrile</td>
<td></td>
</tr>
<tr>
<td>11 F 3</td>
<td></td>
<td>8 PEA 3 Clonic Daily</td>
<td></td>
<td>4b 4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>OC 7 s</td>
<td>PEA 8 s</td>
<td></td>
</tr>
<tr>
<td>12 F 5</td>
<td></td>
<td>42 RAS 108 Clonic</td>
<td></td>
<td>4a 1</td>
<td>Pacing</td>
<td>–</td>
<td>–</td>
<td>Tilt 30 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 M W 11</td>
<td></td>
<td>12 BHS 30 Clonic</td>
<td></td>
<td>3 3</td>
<td>Diazepam</td>
<td>OC 1.5 s</td>
<td>Valproate</td>
<td>–</td>
<td>Sister FS with status</td>
<td></td>
</tr>
<tr>
<td>14 F 4 E 11</td>
<td></td>
<td>12 RAS &lt;20 Clonic</td>
<td></td>
<td>3 1</td>
<td>Diazepam</td>
<td>OC 28 s</td>
<td>Diazepam</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 F 11</td>
<td></td>
<td>8 BHS 15 Clonic</td>
<td></td>
<td>4b 3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 F 11 S 7</td>
<td></td>
<td>0.2 RAS 19 Clonic</td>
<td></td>
<td>3 1</td>
<td>Diazepam</td>
<td>CM 20 s</td>
<td>Valproate</td>
<td>Pacing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 M 11 W 11</td>
<td></td>
<td>9 PEA 18 Clonic</td>
<td></td>
<td>4b 3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>OC 0 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 F 11</td>
<td></td>
<td>0.2 RAS 16 Clonic</td>
<td></td>
<td>3 2</td>
<td>Diazepam</td>
<td>OC 15 s</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 M 11</td>
<td></td>
<td>9 PEA 17 Clonic</td>
<td></td>
<td>4b 4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 F 11</td>
<td></td>
<td>120 VVS Total 12</td>
<td></td>
<td>3 3</td>
<td>Diazepam</td>
<td>–</td>
<td>Hair groom</td>
<td>M’s epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 F 11</td>
<td></td>
<td>12 RAS 18 Clonic</td>
<td></td>
<td>3 1</td>
<td>Diazepam</td>
<td>–</td>
<td>Repeat needed</td>
<td>Valproate Same, also FS = FS+</td>
<td>M’s sister FS</td>
<td></td>
</tr>
<tr>
<td>22 F 11</td>
<td></td>
<td>4 BHS 30 Clonic</td>
<td></td>
<td>2c 6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 M E 8</td>
<td></td>
<td>8 RAS 15 Clonic</td>
<td></td>
<td>4b 6</td>
<td>Carbamazepine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 F 8</td>
<td></td>
<td>8 Up to 5/day BHS 3/week</td>
<td></td>
<td>5 3</td>
<td>Diazepam</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 M E 8</td>
<td></td>
<td>14 BHS 20 Clonic</td>
<td></td>
<td>4b 1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 M 0.6 E 11</td>
<td></td>
<td>12 Clonic 15</td>
<td></td>
<td>4a 10</td>
<td>Phenobarb.</td>
<td>–</td>
<td>–</td>
<td>OC 0 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 F 11 E 8</td>
<td></td>
<td>12 Clonic 2</td>
<td></td>
<td>1 Upto 2/ day</td>
<td>Valproate</td>
<td>OC 24 s</td>
<td>PEA 23 s</td>
<td>Twin RAS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All cases were referred from the west of Scotland, except those initialled in the first column as: S, from elsewhere in Scotland; E, from England; W, from Wales, U, from USA. In the second column Ref./case gives the reference and the published case number (if any).

Syncopes are abbreviated: RAS, reflex anoxic seizures/reflex asystolic syncope; PEA, prolonged expiratory apnoea (cyanotic breath-holding); BHS, breath-holding spells of uncertain mechanism or combined asystole and expiratory grunting; VVS, vasovagal syncope of adult type; CVM, compulsive Valsalva manoeuvre.

Under Evidence of epileptic component, the scoring of level of evidence is as in box 1, with “seen in ward”, observed during ward-round; “that’s it!”, recognition of event by parents from video demonstrations; “1/s jerks”, parents described and mimed 1/second jerking.

In Other epileptic seizures: FS, febrile seizures; FS+, febrile seizures plus.

In the last column: FH, family history; M, mother; m, month; the figures before s., seconds refer to duration of asystole; OC, ocular compression; CM, cardiac monitoring; tilt, head-up tilt testing.

Other abbreviations are as previously, except that when PEA is followed by a number of seconds, that is the duration of asystole accompanying the PEA event.
and what followed was simply a clonic epileptic seizure. In support of this assertion is the EEG/ECG appearance of published examples of AES, in particular that of our case 2, as shown in fig 1.

Why some patients have epileptic seizures after synapses while most do not is a most interesting question. It has been known for over 40 years that hypoxia, experimentally induced by nitrogen inhalation, could provoke generalised or focal EEG discharges in adults with respectively generalised or focal epilepsy. Most of the children in our series did not have additional epilepsy—in the sense of recurrent

“spontaneous” epileptic seizures—but four of them (cases 6, 13, 20, and 22) had a family history of probable epileptic seizures, including prolonged epileptic febrile seizures in two cases. In one large family (case 6) there was a history of both infantile epileptic convulsions and PEA, suggesting that an epileptic seizure gene and a neurally mediated syncope gene differ in any identifiable way from the background population of children with neurally mediated synapses. There is little good information on the relative frequency of the different types of infantile syncope, but in a prospective study Lombroso and Lerman found that of their total of 140, 62% had cyanotic breath-holding or what we would now call prolonged expiratory apnoea, 19% had pallid spells (reflex anoxic seizures or reflex asystolic syncope), and 19% were indeterminate. Our series was different, in that asystolic events were more frequent, but not sufficiently so to provide an explanation. We suggest that future combined clinical and genetic studies should address origins of both the syncopal and epileptic components of AES.

In the literature and in our cases, status epilepticus—whether defined as an epileptic seizure lasting 30 minutes or 10 minutes—a frequent complication of AES. Whether this is because AES with only a brief epileptic component are more frequent than AES in any given patient can seldom be prevented, with one important exception: if the syncopal component is RAS, with documented prolonged expiratory apnoea, 19% had pallid spells (reflex anoxic seizures or reflex asystolic syncope), and 19% were indeterminate. Our series was different, in that asystolic events were more frequent, but not sufficiently so to provide an explanation. We suggest that future combined clinical and genetic studies should address origins of both the syncopal and epileptic components of AES.

What this study adds

- In this, the first large systematic study of AES from a single referral centre, the numbers seen suggest that AES—triggered by a variety of synapses—are not rare.
- Clonic status epilepticus—however defined—was common in AES, but was treatable or preventable, whereas the syncopal component could only occasionally be treated.

In conclusion, synapses may trigger true epileptic seizures, and children’s doctors should be aware of this. The paucity of published reports suggests that most AES are either unrecognised or misdiagnosed.

Figure 1 EEG/ECG recording showing AES induced by ocular compression (OC). Each panel lasts about 20 s. In the upper panel OC induces instant asystole and the EEG becomes isoelectric within 1.2 s (the fast deflections in the 9th and 11th channels correspond to down-beat nystagmus). In the centre panel the tonic phase of the anoxic seizure is shown on the ECG line as black “fuzz” due to tonic EMG activity. Midway across the centre panel while the EEG is still isoelectric, rhythmic 2–3/s jerk artefacts are seen on EEG and ECG channels. By the time of the lower panel, rhythmic EEG spike wave is visible, slowing towards the conclusion. Jerking lasted 28 s but the child was unresponsive for a further 8 minutes (reproduced with permission from Stephenson, Mac Keith Press, fig. 11.4).
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An unwell child with a florid rash

A 3 month old girl presented with a striking erythematous rash on her lower limbs. She had become increasingly oedematous and had started to vomit frequently. Despite being breast fed, her stools were frequent, offensive, and pale. Investigations revealed anaemia, hypoproteinaemia, and deranged liver function. Serum zinc levels were normal.

This is necrolytic migratory erythema. In children, it may occur in association with liver disease, inflammatory bowel disease, pancreatitis, and malabsorption syndromes. A deficiency of amino acids, essential fatty acids, and/or zinc is thought to be the cause. Our child was subsequently found to have cystic fibrosis. Creon (pancreatic enzymes) and Ketovite (multivitamins and folic acid) supplementation resulted in a dramatic resolution of the rash and a sustained improvement in the child’s condition.

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Competing interests: none

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