Parental view of epilepsy in Angelman syndrome: a questionnaire study

M Ruggieri, M A McShane

Abstract

Purpose—To explore parents’ opinions and concerns about seizures, anticonvulsants, and the effect of treatment in children with Angelman syndrome.

Design—A postal questionnaire was sent to members of one of the UK lay groups for Angelman syndrome (ASSERT) who had a child affected by Angelman syndrome. The questionnaire requested general medical information and information about the epilepsy, its treatment, and treatment responses.

Results—One hundred and fifty questionnaires were sent out with an ASSERT routine mailing and 78 completed questionnaires were returned. Forty three patients were boys and 35 were girls; ages ranged from 1.7 to 25 years (mean 7.5 years). The overall general clinical and cytogenetic data were mostly consistent with previous reports. Epilepsy was reported in 68 children, most of whom had a detectable cytogenetic deletion. The most common seizure types reported by the families were absence seizures, tonic clonic seizures, drop attacks, and myoclonic seizures; in four patients only febrile seizures occurred. The age at onset of the seizures was < 2 years in more than half of the patients. Anti-epileptic drug treatment with valproate (VPA), clonazepam (CZP), and lamotrigine (LTG) as monotherapy or a combination of VPA and CZP or VPA and LTG was more often viewed favourably and considered effective with fewer side effects on the child’s behaviour and alertness, versus more frequent adverse effects and increased frequency and severity of seizures with carbamazepine (CBZ) and vigabatrin (VGB) in monotherapy or in combination with other anti-epileptic drugs. Seizures did tend to improve with age but were still present and disabling at older ages.

Conclusions—This is the first study to record parents’ opinions about seizures, anti-epileptic drugs, and treatment responses in children with Angelman syndrome, and it is one of the largest series on epilepsy and Angelman syndrome to be reported to date.

(Keywords: Angelman syndrome; epilepsy; seizures; parental opinions; questionnaire

Angelman syndrome\(^1\) (MIM 105830)\(^2\) is a neurogenetic disorder caused by deficiency of gene expression from maternally derived chromosome 15q11–13.\(^3\) Molecular analysis distinguishes four groups of Angelman syndrome patients with the following findings: (1) large (3–4 Mb) maternal deletions of 15q11–13 (60–70%); (2) paternal uniparental disomy (5%); (3) imprinting mutations (2–3%); and (4) non-deletion/non-uniparental disomy/non-imprinting mutations (25–30%). Recent studies\(^5\) have demonstrated a possible abnormality in ubiquitin-associated protein (UBE3/E6-AP) degradation during brain development in Angelman syndrome.

The prevalence of Angelman syndrome has been estimated to be \(\sim 1:10000–200000\).\(^6\) Affected children have severe developmental delay, absent speech or very poor language skills, paroxysms of inappropriate laughter/smiling, hyperactivity, and some distinct facial anomalies such as microbrachycephaly, mid-facial hypoplasia, macrostomia, widely spaced teeth, protrusion of the tongue, alternating strabismus, mandibular prognathism, and signs of hypopigmentation.\(^1\)\(^3\)\(^4\)\(^6\)\(^10\)–\(^14\) Almost all present with a characteristic “puppet-like”\(^9\) motor pattern consisting of ataxic gait, tremulousness, and jerky limb movements, related to a unique pattern of fast bursting cortical myoclonus.\(^15\)

Most children with Angelman syndrome have characteristic electroencephalographic (EEG) abnormalities and a history of convulsions that are difficult to characterise and to manage.\(^1\)\(^4\)\(^6\)\(^10\)–\(^14\) Although there are many reports on clinical and EEG features of seizures in Angelman syndrome,\(^3\)\(^4\)\(^6\)\(^10\)–\(^17\) little is known of the evolution of epilepsy.\(^18\)–\(^25\) On the other hand, to the best of our knowledge, no Angelman syndrome study has specifically recorded parents’ views about their child’s seizures and anticonvulsants, or about the effects of treatment.\(^15\)–\(^25\)

To obtain more information about the incidence and evolution of epilepsy, patterns of seizures, treatment responses, and anti-epileptic drug side effects in children with Angelman syndrome, we performed a study using a parental medical questionnaire in an informed group of families with a child affected by Angelman syndrome, through one of the UK lay groups for Angelman syndrome (Angelman syndrome support education and research trust (ASSERT)).
Table 1 Clinical and cytogenetic features of 78 patients with Angelman syndrome

<table>
<thead>
<tr>
<th>Sex (M/F)</th>
<th>43/35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; range)</td>
<td>7.5 years; 1.7–25 years</td>
</tr>
<tr>
<td>Age at diagnosis (mean; range)</td>
<td>3.3 years; 8 months to 23 years</td>
</tr>
<tr>
<td>Cytogenetic findings</td>
<td></td>
</tr>
<tr>
<td>Molecular deletion at chromosome 15q11–13</td>
<td>53 (30 M; 23 F)</td>
</tr>
<tr>
<td>Uniparental disomy</td>
<td>5 (2 M, 3 F)</td>
</tr>
<tr>
<td>Non-deletion/non-disomy type</td>
<td>9 (4 M, 5 F)</td>
</tr>
<tr>
<td>Data not given</td>
<td>11 (8 M; 3 F)</td>
</tr>
</tbody>
</table>

Patients, materials, and methods

STUDY DESIGN

In June 1996, after completing a pilot parental questionnaire study on 20 families,27 we mailed a questionnaire with an information sheet to the 150 members of ASSERT with a child affected by Angelman syndrome.

The questionnaire requested information about the diagnosis, investigations including cytogenetic data, general health, and common medical and behavioural problems associated with Angelman syndrome, as well as surgical procedures. More specific information about seizures, epilepsy, and treatment was sought using tables and simple questions.

A simplified description of seizure types classified according to the International League Against Epilepsy’s classification of epileptic seizures28 was provided, and parents were asked to attempt to classify their child’s seizures. A list of the commonly available antiepileptic drugs in the UK was given. Parents were asked to complete a simple scoring system on the effect of drugs on fit frequency, severity, and the child’s alertness and behaviour.

Ethical approval for this study was obtained from the central Oxford research ethics committee (COREC).

Results

By November 1996, 78 completed questionnaires were returned. Table 1 summarises the basic composition of the group and their cytogenetic data.

Forty three patients were boys and 35 were girls. Age ranged from 1.7 to 25 years, with an average age of 7.5 years (mean age was 6.5 years for boys and 8.8 years for girls). Age at diagnosis ranged from 8 months to 23 years, with an average age of 3.3 years (mean age was 2.6 years for boys and 4.0 years for girls). Parents reported that the diagnosis was confirmed by a consultant paediatrician, in four by a consultant paediatric neurologist, in three by a neurologist, and in six by other medical specialists; no information was given by one family.

Other than epilepsy, common additional medical problems were squint (n = 40), hearing difficulties related to middle ear infections (n = 44), constipation (n = 37), vomiting (n = 32), scoliosis (n = 15), urinary infections (n = 12), and chest infections (n = 10). No additional medical problems were reported in nine children.

The most common surgical procedures reported were tonsillectomy and/or adenoidectomy (n = 18), placement of middle ear grommets (n = 6), squint surgery (n = 6), inguinal hernia surgery (n = 5), gastrostomy (n = 4), scoliosis correction (n = 3), and tendon surgery (n = 2); 42 patients required no surgery.

Families considered their child’s general health as good or stable in 52 and poor in three. Comments on health were not given by 23 families.

EPILEPSY QUESTIONNAIRE

Epilepsy was reported in 62 (37 boys and 25 girls) of 78 children and in a further four (two boys and two girls) only febrile seizures occurred. Six children (two boys and four girls) had afebrile seizures and were receiving anticonvulsant treatment but their parents did not consider them to be epileptic. No seizures were reported in six patients (two boys and four girls). Seven patients had a family history of epilepsy in a first degree relative. Of the 68 patients with Angelman syndrome and epilepsy or recurrent seizures, 51 had a detectable cytogenetic deletion.

Of the patients with Angelman syndrome and epilepsy or recurrent seizures, 65 families attempted to classify seizure types, and recorded seizure frequency, treatment, and treatment responses. Seizures of several types were reported (table 2). Seventy five children had had more than one recorded EEG.

The age at onset of the seizures was < 2 years in 43 patients and > 2 years in 25 patients, with an average age at onset of 20 months.

Of the 68 children with seizures, 45 had their last fit in the month preceding the completion of the questionnaire. In nine, the last seizure was longer than two years since completing the questionnaire. In 14 children, no data were given on age at last seizure. Rectal diazepam was given to 47 patients with Angelman syndrome in and in 13 patients it was used more than two to three times during the preceding year.

Fifty families recorded their child’s current treatment: among these 50 patients valproate (VPA) was used in 13, clonazepam (CZP) in three, clobazam in three, lamotrigine (LTG) in one, a combination of VPA and CZP in 10, a combination of VPA and LTG in eight, a combination of LTG and CZP in three, and a combination of CZP and clobazam in one; five patients were taking a combination of three of the aforementioned drugs. Seizure control was
reported as good (stable or poor) and seizure evolution as improving (stable or deteriorating) in patients on VPA (12/13), CZP (3/3), clobazam (2/3), LTG (1/1), VPA and CZP (10/10), VPA and LTG (7/8), VPA and ethosuximide (1/3), LTG and CZP (3/3), clobazam and CZP (1/1), and in four of five patients on triple treatment usually with VPA and a benzodiazepine in addition to other antiepileptic drugs.

The effects of individual drug treatment on seizures and the child's alertness and behaviour are shown in table 3. Factors with a negative effect on seizures were fever, illness, and tiredness. The epilepsy in one child was reported to improve with the ketogenic diet. The most reported side effects were drowsiness and tremor when using VPA and drooling when using CZP.

Parents reported that puberty was associated with overall seizure improvement in three, deterioration in one, and no effect in two patients; data was not given by 14 families with a child at or over 11 years.

One child died at age 4 years as a result of poorly controlled epilepsy.

Discussion
The overall clinical and cytogenetic data of the 78 patients presented here are mostly consistent with previous reports.

Our patients could be divided into the major types of Angelman syndrome, namely, patients who were deletion positive (53), patients with uniparental disomy (5), and non-deletion/non-disomy-type patients (9) (table 1). This suggests that our sample was representative of most other Angelman syndrome populations studied.

We found that Angelman syndrome becomes a more frequent diagnostic consideration between 1 and 4 years of age, as confirmed by other studies. The average age at diagnosis was lower in boys than in girls, a previously unreported observation in large series of patients with Angelman syndrome.

Many of our patients had associated medical problems and a significant number required surgery for these problems. Zori et al found similar problems in most of the British patients with Angelman syndrome but in none of the American patients.

The overall reported prevalence of active epilepsy and recurrent afebrile seizures in our patients was similar to other reported series, with most of our patients with epilepsy having a detectable cytogenetic deletion. Also, seven patients had a family history of epilepsy in a first degree relative.

The age at onset of seizures in our group was similar to previous studies of Angelman syndrome, which show that seizures had an onset at age 1–3 years in most patients with Angelman syndrome and at < 12 months in 14%. The most common seizure types reported by parents in our group were absence seizures, tonic-clonic seizures, drop attacks, and myoclonic seizures (table 2). A few parents reported episodes suggesting non-convulsive status in their child and only a small percentage of them had infantile spasms, convulsive status, and complex partial seizures. The most frequent type of seizures in previous studies on Angelman syndrome were tonic-clonic seizures, atypical absence seizures, myoclonic seizures, tonic seizures, and status epilepticus in childhood; absence status and myoclonic status epilepticus were also found.

In adulthood, atypical absence seizures, myoclonic seizures, or a combination of the two are the most prominent, as was reported in our four adult patients with Angelman syndrome.

The use of rectal diazepam in our group suggests that epilepsy was an important problem in 47 of the 68 patients with epilepsy and was severe in a further 13. Of note, one in 10 patients were on treatment with three antiepileptic drugs, where current treatment was recorded.

In our group, anti-epileptic drug treatment with VPA, CZP, and LTG in monotherapy or a combination of VPA and CZP or VPA and LTG was more often viewed favourably and considered to be effective. No specific drug or any combination of drugs was reported to be superior in seizure control in the study by Zori et al, VPA as monotherapy or combined with clobazam proved effective in the control of both isolated seizures and myoclonic status epilepticus in the series of Viani et al.

In the study of Laan et al the most effective anti-epileptic drugs were phenobarbitone (PB) in monotherapy or VPA in combination with CZP or other benzodiazepines; in adult patients with Angelman syndrome, PB has also been shown to be effective. It is of note that piracetam used in association with VPA or benzodiazepines was shown to be an effective and safe drug for symptomatic treatment of cortical myoclonus in five of 11 patients reported by Guerrini et al, resulting either in a reduction in myoclonus or improvement in dystonic limb posturing and ataxic gait. None of our patients used piracetam.

In our series, seizures were considered to be increased in frequency and severity with adverse effects reported more frequently with carbamazepine (CBZ) or vigabatrin (VGB) in monotherapy or in combination with other drugs (table 3). It is of note that a similar effect of CBZ on seizures was reported by previous
authors but not for VGB. Conversely, seizures in our group were considered to be controlled in frequency and severity by using VPA, LTG, CZP, clobazam, and nitrazepam (NZP) in monotherapy or combined. Parents recorded less side effects on their child’s alertness and behaviour with LTG, CZP, clobazam, and NZP than with VPA (table 3).

Epilepsy in our group did tend to improve with age; nonetheless, only about half of the older patients (12 of 20 at age > 10 years) reported overall improvement with time (seizures improvement v static or deteriorating seizures). Furthermore, the four patients older than 20 years in our series were reported not to be free from fits. A few previous studies reported that seizures reduce in Angelman syndrome with age and are more easily controlled in later childhood but more recent, larger surveys have found that 92% of the adult patients with Angelman syndrome continue to have epileptic seizures and that seizures play an important role in daily life.

As expected, we found that fever, illness, and tiredness were the most common triggering factors for seizures. It is of note that one child in our series was taking the ketogenic diet and that this diet was effective in improving seizures in this patient.

Overall, the powerful anticonvulsant and anti-absence actions of benzodiazepines, which are based on their GABAergic properties, were also seen in our patients with Angelman syndrome. In contrast, new anti-epileptic molecules designed for enhancing GABAergic inhibition such as VGB (GABA-T blocker) were not so effective in treating Angelman syndrome associated seizures, as shown in experimental and clinical models of absence seizures.

We acknowledge that this is a selected patient group but hope that the number of responses make the observations useful. The questionnaire was long and relatively complicated but was completed adequately by most parents. The method of distributing the forms combined with their relative difficulty probably accounts for the high number of non-returns; however, the clinical and genetic data provided by parents suggest that this is a representative group of Angelman syndrome patients.

We thank all the parents for enthusiastically filling in the questionnaires. Mr R Allen and Mr A Pryor from ASSERT are gratefully acknowledged for their considerable help and support.

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