

# Letter to the editor

## 'Efficacy of different antiepileptic drugs in children with Angelman syndrome associated with 15q11-13 deletion: the Danish experience'

SIR—Angelman syndrome (AS) is a neurogenetic disorder with severe mental retardation\*, absent speech, inappropriate laughter, characteristic facial appearance, a movement disorder, seizures, and characteristic abnormal EEG activity.<sup>1</sup> AS can arise from the following molecular genetic defects: a maternal deletion in 15q11-13 (70%), mutations that alter imprinting (2–3%), and paternal uni-parental disomy (5%) for the region. Another 20–25% of individuals with clinical symptoms of AS have none of these three defects but are believed to have mutations in one or more genes in the region; the UBE3A gene has been found to be mutated in some patients.<sup>2</sup> Patients from all genotypic classes show the characteristic EEG-pattern, but those with a maternal chromosome 15q11-13 deletion suffer more severe epilepsy.<sup>2</sup> In spite of the predominant role of epilepsy in AS, no randomized studies of antiepileptic drug treatment exist. Case reports<sup>3–6</sup> and a retrospective study using a parental questionnaire<sup>7</sup> have reported an increase in frequency and severity of epilepsy using carbamazepine and vigabatrin.

In order to obtain more information of the efficacy and adverse effects of antiepileptic drugs used in AS, we performed a descriptive retrospective cohort study comprising all 20 children in Denmark with a known and proven 15q11-13 deletion. The following parameters were obtained from the medical files: age at first seizure, age at diagnosis of AS, name and dosage of antiepileptic drugs administered and description of seizure types according to the International League Against Epilepsy's classification of epileptic seizures.<sup>8,9</sup> The effect of treatment was allocated into five groups: seizure free; >50% seizure control; <50% seizure control; unchanged; or worsened – all within three and six months of treatment. Ethical approval was obtained from the Danish Research Ethics Committees.

The age distribution of the 20 participants was 2.8 to 14.1 years (mean 8.3 years). The diagnosis was confirmed by demonstration of the 15q11-13 deletion between the age of 6 months and 11 years (mean 4 years). Seizures were noted in all 20 patients and in 17 patients onset was before 2 years of age. All but two children had more than one seizure type: absences or atypical absences being the most frequent. Up to six different antiepileptic drugs were administered to each patient, with a maximum of three drugs at a time. The response of the different antiepileptic drugs is summarized in Table I. In 11 cases, valproate was the first drug administered. Four of these patients became seizure-free and a more than 50% reduction was achieved in another four patients. No improvement was noted in three children, but worsening was not reported. Of five patients treated with valproate on an add-on basis, more than a 50% reduction in seizure frequency was achieved in three instances. Mild sedation was reported in one child.

Nitrazepam was given as monotherapy in two patients and as add-on therapy in six patients. 'Seizure freedom' was achieved in seven of the eight patients. The dose was relatively low: 0.1–0.25 mg/kg/24 hour and mild sedation was reported in only one child. Similar positive antiepileptic effects and very rare side-effects occurred using clobazam and clonazepam.

In all nine children treated with carbamazepine or oxcarbazepine, an increase in seizure frequency and severity was reported. In six of the patients, atonic seizures were provoked or worsened and in three patients the parents reported an almost total loss of visual and social contact with their children. The increase in seizure frequency and the lethargy appeared during the initial weeks of treatment. In some of these patients, a second or third drug was administered with a moderately positive effect. After periods of varying duration, carbamazepine or oxcarbazepine was withdrawn and was followed by prompt improvement in alertness and decrease in severity of seizures.

In all three patients treated with vigabatrin, an onset of treatment was followed by increase in seizure frequency and severity. In two children lethargy appeared and in one child a myoclonic status appeared. The adverse effects promptly disappeared after discontinuation of vigabatrin.

AS was diagnosed in a female infant by genetic analysis when she was 18 months old, two months before her first generalized tonic-clonic seizure. Soon after initiating oxcarbazepine treatment, her parents observed a steadily increasing number of atonic seizures and long-lasting periods of apathy. She lost some of her previously established motor skills and eye contact became almost impossible to achieve. Two months later, valproate was supplemented and an increase in alertness was observed, but still the parents found her capacity for emotional contact compromised and she continued having daily atonic and myoclonic seizures. On withdrawal of oxcarbazepine her capacity for emotional contact was re-established. Her motor skills steadily increased but as atonic and absence-like seizures were still seen, nitrazepam was added. On nitrazepam (0.15 mg/kg/24 hours) and valproate (33 mg/kg/24 hours) she was seizure-free for more than two years except for short atonic seizures during febrile illness.

In the present series, seizures were increased in severity and frequency, and some children became severely lethargic when vigabatrin, carbamazepine, or oxcarbazepine were administered. Similar adverse effects have been reported in other cases with 15q11-13 deletions<sup>3–6</sup> as well as in a patient with an imprinting mutation.<sup>2</sup> Carbamazepine and oxcarbazepine probably act by inhibiting ion conductance through fast sodium channels, but the pathophysiology behind worsening of seizures with carbamazepine and oxcarbazepine in AS patients remains speculative. As no worsening of seizure was seen, valproate seems to be safe in AS.

Some of the genes within the deleted 15q11-13 region code for a cluster of three GABAA receptor subunits. GABRB3 is the most centromeric of the three GABAA receptor subunit genes<sup>10,11</sup> and it was the only deleted receptor subunit gene in four children with AS from two different families with overlapping microdeletions (approximately 1 MB) encompassing UBE3A and a part of GABRB3.<sup>11–13</sup> This suggests that loss of the GABRB3 gene predisposes the

\*US usage. UK usage: learning disability

child to the more severe epilepsy in 15q11-13 deleted AS patients.<sup>2</sup> The powerful GABAergic antimoynoclonic and anti-absence actions of benzodiazepines seen in this study of 15q11-13 deleted children with AS support this hypothesis. Concordant is a recent report of a good response to topiramate, a drug with GABA-mimetic effects.<sup>14</sup>

In conclusion, our study confirms that nitrazepam, clobazam and clonazepam are very effective drugs in AS. Treatment with carbamazepine, oxcarbazepine, or vigabatrin was followed by an increase in seizure frequency and severity and should be avoided in AS.

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**Table I: Twenty patients with Angelman syndrome associated with 15q11-13 deletion. Number of monotherapies and add-on therapies and response to therapy within 6 months**

AED	Mono-therapy	Add-on therapy	Number of therapies	Seizure free	>50% reduction	<50% reduction	Unchanged	Worsened
VPA	11	5	16	4	7	0	4	0
NTZ	2	6	8	7	1	0	0	0
CLN	2	3	5	4	0	1	0	0
CLB	1	3	4	4	0	0	0	0
ETH	0	3	3	2	0	0	1	0
LTG	0	2	2	0	0	0	1	1
OXC	3	2	5	0	0	0	0	5
CARB	3	1	4	0	0	0	0	4
VGB	0	3	3	0	0	0	0	3

AED, antiepileptic drug; VPA, valproate; NTZ, nitrazepam; CLN, clonazepam; CLB, clobazam; ETH, ethosuximide; LTG, lamotrigene; OXC, oxcarbazepine; CARB carbamazepine; VGB, vigabatrin