Epilepsy with myoclonic absences

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Abstract

The cases are described of eight children, five of them girls, who had epilepsy with myoclonic absences. The mean age of onset was 4.9 years. Brief episodes of loss of awareness with bilateral clonic jerking of the upper limbs were associated with rhythmic 3 cycles/second spike-wave discharges on electroencephalogram. Generalised tonic-clonic or astatic seizures, or both, also occurred in seven patients. All now have learning difficulties, and seven have behavioural problems. Conventional treatment for absences was effective in only two children. Of six patients treated with lamotrigine, five have improved substantially, but only one is in sustained complete remission. One recently diagnosed patient continues to have frequent myoclonic absences. As the response to treatment and long term outcome are much poorer, it is important to differentiate myoclonic absences from typical childhood absence epilepsy.

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Epilepsy with myoclonic absences is a rare type of childhood epilepsy in which intellectual impairment and resistance to treatment are usual.¹ We wish to draw attention to this syndrome, as unlike childhood absence epilepsy, it has a poor prognosis. The electro-clinical features of eight children with myoclonic absences are described. Their responses to conventional antiepileptic drugs, and the new drug, lamotrigine, are discussed.

Patients and methods

Eight patients with myoclonic absences attended the paediatric neurology clinic at the University Hospital of Wales between 1983

and 1993. All came as tertiary referrals for difficult to treat epilepsy. For each child detailed histories of development and seizures were obtained and full neurological examinations performed. Myoclonic absences were often observed during the clinical examination. Electroencephalograms (EEGs) were recorded at rest and during hyperventilation and photic stimulation. Previous and current antiepileptic drugs were noted. Three of the children were studied during an add-on trial of lamotrigine in treatment resistant seizures,² and a further three have subsequently received lamotrigine.

Results

Table 1 gives the characteristics of the children. All but patients 6 and 8 were referred at least one year after the onset of myoclonic absences. The mean age at onset was 4.9 years. There were five girls and three boys. Patients 3 and 4 are siblings; of the others, febrile seizures have occurred in siblings of patients 1, 6, and 7, and epilepsy with generalised tonic-clonic seizures on awakening in a sister of patient 2. No child had severe learning difficulties before onset, but four were recognised as requiring special help with education at the time of school entry. Seven currently receive remedial teaching or are in special units within mainstream schools; patient 3 has moderate learning difficulties and is educated in a school for slow learners.

The myoclonic absences were of abrupt onset and offset and could be precipitated by hyperventilation in seven of the patients. Patient 2 was unable to cooperate with over-breathing. Two of the children were aware of the attacks, one referring to them as 'shivers'. During myoclonic absences, rhythmic bilaterally synchronous small range clonic jerking of the head and upper limbs was seen in association with a loss of awareness. In patient 2, the eyelids were also affected. Occasional incontinence was reported. Patients 1-4 kept seizure diaries before being placed on lamotrigine. Myoclonic absences were recorded between five and 80 times daily. The frequency of myoclonic absences was extremely variable in patient 6. Table 2 gives the estimated frequencies for all patients. The parents reported an increased number of myoclonic absences during periods of ill health or tiredness. Myoclonic absences tended to be most prominent soon after awakening. Epileptic falls occurred in patients 1 and 5, in association with more violent jerking, and in patients 3, 7, and 8 without being preceded by obvious myoclonias. Generalised tonic-clonic seizures occurred only once or twice in a year in patients 1 and 4, up to three times a

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Table 1 Characteristics of patients with myoclonic absences

	Patient No							
	1	2	3	4	5	6	7	8
Current age (years)	13	9	14	16	7.5	15.8	9.2	6.2
Age at onset of myoclonic absences (years)	3.5	7.5	4	6	3.5	0.9	7.5	6
Sex	F	F	F	M	F	M	M	F
Family history of seizures	+	+	+	+	-	+	+	-
Development before myoclonic absences	N	D	D	N	N	N	D*	D
Associated seizures								
Generalised tonic-clonic	+	-	+	+	-	+	+	-
Astatic	+	-	+	-	+	-	+	+
Preceding febrile seizures	+	-	-	-	-	-	+	-
Neurological status								
Ataxia	+	+	+	+	±	+	±	-
Dyspraxia	+	+	+	+	+	±	-	+
EEG								
Normal background	+	+	+	+	+	+	+	+
Ictal generalised 3 c/s spike-wave	+	-	+	+	+	+	+	+
Ictal 2-3 c/s spike-wave	-	+	-	-	-	-	-	-
Photosensitivity	-	+	-	-	-	-	+	+

+ = Present; ± = minimally present; - = absent. F = female; M = male; N = normal; D = delayed.

*Delay in speech and language only.

Table 2 Myoclonic absences: summary of responses to treatment

	Patient No							
	1	2	3	4	5	6	7	8
Maximum number of myoclonic absences each day	12	80	18	5	40	See text	60	15
Treatment*								
ESM alone	NR	NR	NR	NR	NR	NR	—	—
VPA alone	NR	NR	NR	NR	NR	NR	NR	R
ESM + VPA	NR	NR	NR	NR	NR	R	—	—
ESM + VPA + CZP	NR	—	—	NR	—	—	—	—
ESM + CZP	—	NR	—	—	—	—	—	—
CZP alone	—	—	—	—	—	—	NR	—
CBZ alone/combined	NR	NR	—	—	—	See text	NR	—
PHT alone/combined	—	—	NR	NR	—	—	NR	—
GVG combined	—	—	—	—	—	—	NR	—
LTG + VPA + ESM	R	—	R	R	—	—	—	—
LTG + ESM + CZP	—	R	—	—	—	—	—	—
LTG + VPA	—	—	—	—	R	—	—	—
LTG + GVG	—	—	—	—	—	—	NR	—
Prednisolone	—	—	—	—	—	—	NR	—
Ketogenic diet	—	—	—	—	—	—	NR	—

NR=no response; R=at least 75% reduction in myoclonic absences. *ESM=ethosuximide; VPA=valproate; CZP=clonazepam; CBZ=carbamazepine; PHT=phenytoin; GVG=vigabatrin; LTG=lamotrigine.

month in patient 7, and almost every night in patient 3. Patients 6 and 7 had had serial myoclonic absences lasting from one to several hours. The seizure history was unusual in patient 6. Myoclonic absences started in the latter part of the first year, continued until the age of 3 years when remission occurred during treatment with carbamazepine, but the attacks recurred at the age of 8.5 years. Two children had earlier had brief generalised febrile seizures.

The EEGs in all patients showed normal background rhythms. In seven, the myoclonic absences were accompanied by rhythmic 3 cycles/second (c/s) spike-wave. In patient 2, the abrupt onset of myoclonic absences was associated with 2 c/s spike-wave activity, rapidly accelerating to 3 c/s spike-wave by the end of the attack. Additional brief episodes of bilateral spike-wave were often seen and in three patients focal spike-wave discharges were also observed.

All except patient 8 had some evidence of cerebellar ataxia, mainly manifest when attempting movements requiring precision. The ataxia tended to be worse when seizure control was poor. Seven children were dyspraxic, three of them severely so. General examination was normal in seven, but patient 2 had mild microcephaly and bilateral under-development of the mandibular condyles and a ventricular septal defect which closed spontaneously.

Behavioural problems have been prominent in five patients and mild in a further two. Restlessness, difficulties with complying with instructions, and impulsiveness are the main complaints. Patient 6 was aggressive in early adolescence and patient 3, the least intelligent of the cohort, was defiant and tended to wander from home and indulge in irresponsible behaviour.

Table 2 summarises the therapeutic regimens used. Valproate alone has been effective only in patient 8, whose myoclonic absences started within two months of referral and whose current period of follow up is short. No patient responded to ethosuximide alone and only one to a combination of valproate and

ethosuximide. The addition of clonazepam was unhelpful, as were prednisolone and a ketogenic diet in the one patient receiving these. Patient 6 had an apparently complete remission while receiving carbamazepine. This lasted for five years, during which a single EEG recorded no abnormalities. On relapse, carbamazepine did not reduce the frequency of myoclonic absences. There were then considerable problems with compliance before a further remission occurred during treatment with valproate and ethosuximide. Patient 6 has been completely seizure-free since the age of 13 years. None of the other patients treated with carbamazepine, phenytoin, or vigabatrin responded to treatment. Patients 1, 3, and 4 were treated with lamotrigine in an add-on trial starting in 1987. It was soon clear that their myoclonic absences were becoming much less frequent. Patients 1 and 4 have had at least six months of complete freedom from myoclonic absences. Patient 1 remained without myoclonic absences during the withdrawal of concomitant ethosuximide and clonazepam, but relapsed when an attempt was made to also withdraw valproate. The reintroduction of valproate led to some improvement, but infrequent myoclonic absences are still occurring. Patient 4 remains free of myoclonic absences when well and complying with treatment, but he relapses when unwell and does not always comply fully. Patient 2 received lamotrigine in addition to ethosuximide and clonazepam with the gradual reduction of myoclonic absences and, after six months, complete remission, which has continued to date (nine months). Patient 3 has continued to have occasional myoclonic absences during six years of treatment with lamotrigine. Patient 7 has been referred to the University Hospital of Wales only recently and was having many myoclonic absences during treatment with lamotrigine and vigabatrin; currently vigabatrin is being withdrawn and valproate introduced.

Discussion

Epilepsy with myoclonic absences was recognised as an individual syndrome in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy.³ The features have been most clearly delineated by Tassinari *et al*,¹ who have reported the clinical and EEG findings in 36 patients. The syndrome is rare, being found in between 0.5 and 1% of patients referred to a specialist epilepsy centre.¹ Most patients are referred to the paediatric neurology service in Cardiff by paediatricians or paediatric neurologists. About 90 new referrals for epilepsy are seen each year, suggesting that eight patients with myoclonic absences over 11 years is similar to the number expected. The age at onset in this series is younger than that previously described and girls outnumber boys, unlike earlier series.¹

The generalised, rhythmic 3 c/s discharges on EEGs during myoclonic absences are indistinguishable from those of typical absence

epilepsy of childhood.¹ All but one child in this series was initially considered to have typical absences. The importance of observing attacks cannot be overemphasised, as the upper limb myoclonias, only rarely associated with eyelid jerking, can be early alerting features to a more serious form of epilepsy. Spontaneous attacks or episodes induced by hyperventilation were observable in the clinic in all patients in the current series. Generalised tonic-clonic seizures and epileptic falls are commonly part of epilepsy with myoclonic absences¹ and were present either singly or together in all but one of our patients. Although ictal EEGs all showed bilaterally synchronous 3 c/s spike-waves and three patients were photosensitive, focal spike-waves were also seen in three patients. The presence of focal or multifocal spike-waves or spikes was noted in 14% of patients of Tassinari *et al*, who also reported that in 25% of their patients the motor manifestations were asymmetrical.¹ Asymmetry of clinical attacks was not observed in our patients, but none had simultaneous electro-myographic and EEG recordings, which would facilitate the identification and quantification of motor activity. Photosensitivity was found in five (14%) of 36 and three (33%) of eight of the previous¹ and present series respectively.

Neurological and cognitive problems are rare in typical absence epilepsy.⁴ In contrast, in children with myoclonic absences, a delay in development is common before onset. At presentation, four of eight children in our series and 44% of those reported previously¹ were already recognised as having learning difficulties. Cognitive arrest or deterioration was observed after the onset of myoclonic absences in a further 25% of the previous series, leaving 69% of the 36 children mentally retarded.¹ All four children in our series who were initially considered to be normal in development have had difficulties at school, requiring remedial help or transfer to special classes within a mainstream school. Clearly myoclonic absences are less benign than typical absence seizures.

Genetic factors appear to be important in our series, where six of the eight patients had a first degree relative with febrile or other seizures. It has been suggested previously that febrile seizures are not a related disorder.⁵ Five of our eight patients had siblings thus affected, however. Only one further patient reported a family history of epilepsy, which was more common, at 19%, in the previous series.¹

Resistance to conventional treatment for absences is an almost constant feature of myoclonic absences and was the reason for referral in all eight of our patients. Valproate and ethosuximide in combination led to remission in seven (19%) of the 36 patients of Tassinari *et al*¹ and in one (13%) of eight in our series. Previous patients have responded

to various combinations of valproate, benzodiazepines, ethosuximide, and phenobarbitone.¹ The combination of valproate and ethosuximide, with good compliance confirmed by plasma monitoring, did not influence myoclonic absences in five of our patients. The remission of patient 6, confirmed by EEG, while taking carbamazepine alone is unexpected. We have been impressed by the effect of lamotrigine. In five patients useful reductions in myoclonic absences have been achieved and three have had total remissions, unfortunately not sustained in two, lasting for several months. It remains to be seen whether discontinuing vigabatrin, which may exacerbate myoclonic seizures,⁶ and introducing valproate will lead to improved control in patient 7.

The long term outlook for patients with myoclonic absences is not well defined.¹ In none of our patients has the epilepsy evolved to the Lennox-Gastaut syndrome, though this has been reported previously.¹ The continuation of seizures, mild to moderate learning difficulties, and, for most of our patients, restless and problematic behaviour has made appropriate social integration difficult. For the younger children who have responded to lamotrigine, the outlook might be less bleak.

In conclusion, epilepsy with myoclonic absences has distinctive characteristics which allow its separation from typical childhood absence epilepsy. Recognition of the likelihood of resistance to conventional drugs for absences, cognitive impairment, and poor social adjustment should make appropriate counselling possible early in the evolution of the disease. Treatment with lamotrigine, probably better used with valproate or valproate and ethosuximide than alone, seems to be more effective than other drugs, but further studies are required.

Addendum

Since submitting the paper, patient 7 has had his medication revised and he is now free of myoclonic absences on a combination of lamotrigine and valproate.

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