REGULAR REVIEW

Infantile spasms

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Infantile spasms represent a seizure disorder with unique clinical and electroencephalographic (hypsarrhythmia) features and a poor prognosis including chronic intractable epilepsy and psychomotor retardation. The association of spasms and hypsarrhythmia, with or without mental retardation, defines West's syndrome. West's syndrome is not uncommon; the incidence is considered to be 0.16–0.42 per 1000 live births.¹ In 1991, over 760 000 live births occurred in England, Wales, and Scotland (Office of Population Censuses and Surveys, personal communication) giving an estimated number of 122 to 319 new cases of West's syndrome each year. In the 150 years since the original description, there has been little progress in the understanding of the pathophysiology of the spasms, although some advance has been made in their classification and aetiology. Treatment has remained essentially empirical, but there is increasing evidence that the newer antiepileptic drugs and even surgery may be of benefit. This paper reviews the current 'understanding' and areas of future development in this seizure disorder.

The spasms

Spasms were originally reported in 1841 by Dr West in his own 4 month old son; his detailed description remains unsurpassed and should be read.² Spasms may develop between 1 day and 5 years of age,³ but the vast majority of children have an onset between the ages of 4 and 9 months^{4 5}; 90% begin within the first year of life. Boys appear to be more frequently affected by a ratio of approximately 1.3:1.^{5 6} Synonyms include lightning or jackknife convulsions and salaam seizures. A spasm is due to a sudden muscular contraction that is usually generalised but may be asymmetrical, involves muscles of the neck, trunk, and limbs and is accompanied by a brief loss of consciousness. The spasms are usually very brief and transient (myoclonic), or less commonly more sustained (tonic), lasting a few seconds. The most common seizure pattern is mixed flexor and extensor.⁷ Where the spasm is massive, and flexor the infant may double over and cry out, which may lead to a misdiagnosis of colic.⁷ In other infants the spasms may be subtle, such as a slight head nod, or even a momentary upward deviation of the eyes and eyelids, which may also delay diagnosis. Conversely, there are other, non-epileptic paroxysmal

disorders that may be mistaken as spasms,⁸ including benign infantile sleep myoclonus, opisthotonic posturing due to spasticity, and gastro-oesophageal reflux. At the onset, spasms may be infrequent and occur singularly; however, within days, the spasms occur in clusters particularly upon awakening or on falling asleep. The clusters may consist of as few as five, or as many as 100 spasms with between three and 30 seconds between each spasm and may be followed by irritability and crying, lethargy, and drowsiness.⁵ This clustering of spasms is almost unique to this age group and tends to diminish over a period of months, disappearing in most children by the age of 2 years. In older children each spasm lasts longer and represents more a tonic seizure, one of the characteristic seizure types seen in the Lennox-Gastaut syndrome'.³

The electroencephalogram (EEG)

Hypsarrhythmia is the characteristic EEG pattern seen in children developing spasms in the first year of life, and was recognised in the early 1950s.⁹ It consists of high voltage (greater than 200 microvolts) and multifocal spikes, spike and wave discharges, chaotic slowing, and asynchrony. This activity may occur continuously or in bursts, may be absent in the waking state appearing only in non-rapid eye movement (non-REM) sleep, and disappearing in REM sleep. A sleep recording should therefore be obtained in infants suspected of having spasms particularly if an initial, or 'awake' EEG is non-specifically abnormal. The occurrence of a spasm during an EEG is frequently associated with a relative flattening (attenuation) or suppression of the trace, rather than by a spike discharge.⁷ Hypsarrhythmia is usually generalised but may be asymmetrical or even unilateral.^{10 11} It is rarely seen after the age of 3 years. The pattern of hypsarrhythmia may be used prognostically in certain children, although there is no clear relationship.⁷ Unilateral or grossly asymmetrical recordings (which may represent a persistent focal lesion) are associated with a poorer outcome, in contrast to 'typical' symmetrical patterns, where the response to treatment and prognosis are more favourable. Less abnormal patterns of hypsarrhythmia are also reported to have a better outcome. The degree of 'abnormality' of a hypsarrhythmic record is difficult to define, is frequently subjective and may simply reflect the patient's age; in the

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author's experience there is no correlation between outcome and degree of abnormality.

Associated clinical features

Mental retardation is common in West's syndrome and may precede the onset of spasms in approximately 70% of patients^{12 13}; this figure may be greater as mild developmental delay may be difficult to identify, particularly retrospectively. Eventually almost 90% of children will manifest some degree of mental retardation.¹³ In previously well or 'normal' children, there may be a plateau, or even regression in development. Children are hypotonic and visually inattentive and may therefore be considered to be visually impaired. Even in children with abnormal development before the onset of spasms, the development of seizures is frequently reflected in a definite regression. An arrest in development may be the presenting feature in those infants with subtle spasms. Once the spasms resolve, developmental progress may be resumed, although this is not invariable and depends on both the underlying cause and response to treatment.

Disorganised sleep is also frequently associated with infantile spasms,^{5 14} as manifest by a reduction in both total sleep but also REM sleep.¹⁴ The disturbed REM sleep pattern appears to be related directly to the frequency of spasms at least in some patients, as electro-clinical suppression of the spasms by steroid treatment is accompanied by an increase in REM sleep.¹⁴ This apparent association between spasms and REM sleep has led to speculation about a common pathogenesis involving the pons, or other brainstem structures.¹⁴

Classification of spasms

It is in the terminology and classification of spasms that some progress has recently been made.¹⁵ Firstly, the seizure type classically termed infantile spasms typically occurs in infancy where it is usually associated with hypsarrhythmia (West's syndrome) but may also occur in later childhood where it may occur as part of a chronic epilepsy syndrome. This has implications for the International League Against Epilepsy (ILAE) 1989 classification where infantile spasms is synonymous with West's syndrome and listed in the generalised cryptogenic or symptomatic epilepsies (age related)¹⁶; it is proposed that in addition to this syndrome classification, 'spasms' should be included as a specific seizure type which may occur outside West's syndrome. Secondly, 'infantile spasms' (in this context referring directly to spasms occurring in infancy with hypsarrhythmia, that is West's syndrome) may be classified according to aetiology, into symptomatic, cryptogenic, and idiopathic cases.¹⁷ The symptomatic group is characterised by the existence of neurological dysfunction (for example psychomotor retardation, or earlier seizures) before the onset of spasms with a known aetiology, and the cryptogenic group by the prior existence of

neurological dysfunction *without* a demonstrable cause. The much smaller idiopathic group is defined by normal development before the onset of symmetrical spasms, normal examination, normal computed tomography and magnetic resonance imaging, hypsarrhythmia, and absence of any focal EEG abnormality.¹⁵ The acceptance of this idiopathic group is not universal and probably constitutes only a very small proportion of all infants with West's syndrome. Clearly, the definition of the symptomatic and cryptogenic groups is dependent upon the number and degree of sophistication of investigations. The advent of first computed tomography and then magnetic resonance imaging has clearly resulted in an altered proportion of symptomatic versus cryptogenic cases. The development of functional brain imaging such as positron emission tomography¹⁸ may, theoretically, identify additional symptomatic cases, although this technique is obviously not ubiquitous, and is restricted to only a few centres within the UK. Finally, the use of simultaneous video-EEG monitoring has led to a much more precise characterisation of infantile spasms in terms of clinical and EEG symptomatology. It is now realised that at least in some children spasms may in fact have a partial onset with rapid secondary generalisation, rather than being always generalised in onset, as previously believed and which is reflected in the 1989 ILAE epilepsy classification.¹⁶

Aetiology and pathophysiology

Infantile spasms have multiple aetiologies that are commonly separated into prenatal, perinatal, and postnatal,^{5 12} depending on the timing of the cerebral insult; prenatal causes are the most common.¹⁹ There is no pathognomic lesion for West's syndrome. It is inappropriate to discuss all causes in this paper; common aetiologies include cerebral dysgenesis or malformations (including tuberous sclerosis and chromosomal disorders) and as a sequel of neonatal hypoxic-ischaemic encephalopathy⁷ (table). Metabolic or toxic disorders and intrauterine infections are not common causes

Aetiology of infantile spasms

Dysgenesis

Tuberous sclerosis, neurofibromatosis, incontinentia pigmenti, Aicardi's syndrome, Sturge-Weber syndrome, cortical dysplasias (including hemimegalencephaly), heterotopias, holoprosencephaly, lissencephaly, and schizencephaly

Hypoxic-ischaemic insult

Prenatal (multicystic encephalomalacia, porencephalies, hydranencephaly)
Perinatal (hypoxic-ischaemic encephalopathy)
Postnatal (cardiac arrest, near drowning)

Haemorrhage and trauma

Perinatal (intraventricular and periventricular haemorrhage)
Postnatal (subarachnoid and subdural haemorrhage)

Infections

Prenatal (cytomegalovirus, toxoplasmosis, rubella, syphilis)
Postnatal (purulent meningitis, cerebral abscess, encephalitis)

Metabolic and toxic

Prenatal (phenylketonuria, non-ketotic hyperglycaemia, hyperornithinaemia, homocitrullinaemia, histidinuria, Leigh's syndrome, pyridoxine (vitamin B6) dependency, sulphite oxidase deficiency)
Perinatal/postnatal (hypoglycaemia, lead toxicity)

Miscellaneous

Cerebral tumour (rarely)

of spasms, but need to be excluded in the initial diagnostic evaluation. The association with pertussis immunisation is unproved, controversial, and probably coincidental.^{20 21} When all children with spasms are considered, between 70 and 75% will be found to have a specific aetiology (symptomatic cases.)¹⁹ A decade ago this number would have been closer to 60%⁵; the improved detection of an underlying aetiology relates primarily to the advent of improved anatomical imaging methods. Magnetic resonance imaging has significantly increased the detection of subtle cerebral dysgeneses such as neuronal heterotopias and other disorders of migration, to the point that it is considered an essential investigation in the evaluation of children with spasms, particularly if an initial computed tomogram is normal.¹⁵

A family history of spasms is uncommon^{12 13}; monozygotic twins may be both concordant and discordant for infantile spasms.²² However, a family history of any epilepsy may occur in 6–17% of cases.¹² No specific genetic marker has yet been identified, and is unlikely to be, but as already stated, infantile spasms may occur in a number of chromosomal/genetic disorders including Aicardi's and Miller-Dieker syndromes and tuberous sclerosis.

The pathogenesis of infantile spasms, as well as the regression in psychomotor development, remains unclear. It is generally believed that spasms are a non-specific response of an immature brain to any insult; however certain insults may be more likely to cause them. Although most insults are multifocal or diffuse in character, unifocal or even unilateral cerebral disorders (for example hemimegalencephaly)¹⁰ may cause spasms. The peak age of occurrence of West's syndrome coincides with the critical period of formation of dendritic spines and myelination that may contribute to the pathogenesis,²³ for which there is some evidence.²⁴ Additional hypotheses include a structural or functional disturbance in subcortical (pontine or lenticular nuclei) neurotransmitter (dopaminergic, serotonergic) pathways; the observation of spasms in an infant with hydranencephaly would support such a mechanism.²⁵ Focal cerebral lesions have also been implicated, and a cortical-subcortical interaction has been proposed to explain how a focal lesion could be responsible for producing generalised, symmetrical spasms.¹⁸ The neuronal circuitry involved is interesting but perhaps simplistic and has implications for both the medical and surgical treatment of spasms.

Treatment

It is in this area that most has been written about spasms, although largely on the basis of retrospective, anecdotal, and predominantly uncontrolled studies.²⁶ Placebo controlled studies have been considered to be unjustified in view of the belief that early diagnosis and treatment determines the long term outcome of late epilepsy and mental retardation.

However, this belief may be ill founded as the ultimate prognosis depends primarily on the underlying aetiology; additional prognostic factors such as pre-existing neurodevelopment status, age of onset, and *response to treatment* are also in fact dependent upon the aetiology and can therefore not be regarded as significantly influencing the outcome per se. Most of the studies have not assessed response to treatment (with whatever agent) in relation to whether the spasms were symptomatic or cryptogenic, or to the underlying aetiology. Although there is limited evidence that at least in the less common cryptogenic (and perhaps particularly in idiopathic) cases, early treatment of spasms is associated with a more favourable outcome,^{13 27} this is not necessarily cause and effect; infants with cryptogenic spasms may be treated earlier than patients with symptomatic spasms because the spasms are recognised earlier. The effect of prompt treatment is thus difficult to separate from that due to the 'severity' of the disorder. Finally there has been little attempt to assess the influence of different periods of treatment lag; most studies report lag periods of months which could arguably be associated with a less favourable response to treatment and outcome. However, a treatment lag of between one and two weeks is unlikely to influence outcome and could therefore be reasonably incorporated into a placebo controlled protocol. There is also an opinion that in some patients spasms may remit spontaneously.²⁸ All of these factors militate against a rational evaluation of treatment of spasms.

However, it does appear to be true that spasms are resistant to many 'conventional' antiepileptic drugs. Most success has been achieved using the benzodiazepines (particularly nitrazepam),²⁹ sodium valproate,^{30 31} corticosteroids and adrenocorticotrophic hormone (corticotrophin, ACTH).³² High dose pyridoxine³³ (vitamin B6), intravenous gammaglobulin,³⁴ and a benzodiazepine-carbamazepine cocktail³⁵ have also been reported to be effective. Vigabatrin, one of the newer antiepileptic drugs has been used to treat spasms initially as 'add-on' treatment³⁶ where it appears to be particularly successful in symptomatic cases (usually the more resistant type), and more recently, as monotherapy,³⁷ where the response has been rapid.

ACTH was first used to treat spasms in the late 1950s³⁸; a recent survey among child neurologists in the United States indicated that of those who responded (only 45%), over 85% used ACTH as the agent of first choice.³⁹ This is in sharp contrast to at least one European country (Dr W F Arts, Professor A C B Peters, the Netherlands, personal communication) and the practice of this author where ACTH is rarely if ever prescribed; others advocate the more selective use of ACTH, in cryptogenic or idiopathic cases. There is much anecdotal evidence but little scientific basis for the use of ACTH or corticosteroids; a recent report has valiantly attempted to explain and rationalise the multiple aetiologies, efficacy of hormonal treatment, and even spontaneous resolution

of infantile spasms.⁴⁰ In addition there is considerable variation in the preparation, dose, and duration of treatment and relapses are common, whether on or off treatment.^{26 41–45} More importantly these drugs are associated with frequent, severe, and potentially fatal side effects. Drug related mortality may be as high as 5%.⁴⁶ ACTH and corticosteroids have also not been shown conclusively to improve the long term outcome of either the development of chronic epilepsy (which occurs in over 65% of children) or mental retardation.^{28 42} Sodium valproate and nitrazepam are additional 'recommended' drugs but are also associated with variable success, relapses, and frequent side effects; nitrazepam is limited by the development of early tolerance and tachyphylaxis. Vigabatrin appears to have considerably fewer and less severe side effects than these recommended treatments and its efficacy may have some recognised neuropharmacological basis⁴⁷; however, there are relatively few data on the use of vigabatrin in infantile spasms and specifically the long term effects of this drug. It is likely that other, newer antiepileptic drugs may also be used to treat spasms, particularly if the initial treatment is unsuccessful.

Finally, surgical resection could (? should) be considered for those children with intractable spasms who are shown to have a unifocal cortical abnormality.^{15 48} Although this should be demonstrated by computed tomography/magnetic resonance imaging and an EEG it may, rarely, require functional (positron emission tomography) rather than anatomical imaging to identify the abnormality.

The psychological impact of the spasms, associated mental retardation, and disturbed sleep on the families of these children may be immense, is always stressful and is frequently devastating. Support for these families is vital but it is usually inadequate and reliant upon the relevant voluntary epilepsy support associations.

Prognosis

Persistence or recurrence of spasms may occur, particularly in those of symptomatic origin (for example cerebral dysgenesis, Aicardi's and Miller-Dieker syndromes).

Factors determining outcome are multiple and are of variable significance.^{7 12 27} In general, cryptogenic/idiopathic cases, a symmetrical hypsarrhythmia, and rapid response to treatment tend to predict a good prognosis; symptomatic cases, a grossly asymmetrical EEG and poor, or no, response to treatment are usually associated with a bad prognosis. The influence of treatment lag is unclear; a delay in treatment of one to two weeks is unlikely to have a detrimental effect on either the short, or long term outcome, whereas a delay of two or more months may arguably adversely affect both the response to treatment and neurological status. The overall prognosis of infants with West's syndrome is poor. Mortality is approximately 5% (both drug and non-drug related), mental retardation occurs in 90% (severe in 70%) of

cases and is often accompanied by motor and behaviour difficulties. Sixty five per cent of children will develop chronic epilepsy, usually the Lennox-Gastaut syndrome or cryptogenic localisation related epilepsy (temporal lobe with complex partial seizures).

Conclusion

The clinical description of spasms has not been improved upon since 1841; the pathogenesis remains unclear and the classification has been revised to include symptomatic, cryptogenic, and idiopathic cases. The development of improved anatomical, and, to a lesser extent functional, brain imaging has identified an increasing number of symptomatic cases. Until recently, the recommended treatment has relied upon drugs that have an unknown mechanism of action and serious side effects.

Infantile spasms (particularly in the context of West's syndrome) demands a more scientifically precise study of its pathogenesis and treatment. This will almost certainly require a multicentre, even multinational collaboration in view of the relatively small numbers of children involved. This practical difficulty should not preclude the evaluation of what is arguably the most malignant epilepsy syndrome/seizure type of childhood. In the interim antiepileptic treatment should be used more rationally and selectively on the basis of the electroclinical pattern and underlying aetiology,¹⁵ and in view of the recent and promising response to the newer antiepileptic drugs.

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- 1 Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. *J Child Neurol* 1991; **6**: 355–64.
- 2 West WJ. On a peculiar form of infantile convulsions. *Lancet* 1841; **i**: 724–5.
- 3 Kurokawa T, Goya N, Fukuyama Y, Suzuki M, Seki T, Ohtahara S. West syndrome and Lennox-Gastaut syndrome: a survey of natural history. *Pediatrics* 1980; **65**: 81–8.
- 4 Jeavons PM, Bower BD, Dimitrakoudi M. Long-term prognosis of 150 cases of 'West syndrome'. *Epilepsia* 1973; **14**: 153–64.
- 5 Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. *Epilepsia* 1983; **24**: 135–8.
- 6 Riikonen R, Donner M. Incidence and aetiology of infantile spasms from 1960 to 1976: a population study in Finland. *Dev Med Child Neurol* 1979; **21**: 333–43.
- 7 Aicardi J. Infantile spasms and related syndromes. In: Aicardi J, ed. *Epilepsy in children*. New York: Raven Press, 1986: 17–38.
- 8 Donat JF, Wright FS. Clinical imitators of infantile spasms. *J Child Neurol* 1992; **7**: 395–9.
- 9 Gibbs FA, Gibbs EL. In: Gibbs FA, Gibbs EL, eds. *Atlas of electroencephalography. Volume 2: epilepsy*. Cambridge, Mass: Addison Wesley, 1952: 24.
- 10 Tjiam AT, Stefanko S, Schenk VWD, de Vlieger M. Infantile spasms associated with hemihypsarrhythmia and hemimegalencephaly. *Dev Med Child Neurol* 1978; **20**: 779–88.
- 11 Alvarez LA, Shinnar S, Moshe SL. Infantile spasms due to unilateral cerebral infarcts. *Pediatrics* 1987; **79**: 1024–6.
- 12 Matsumoto A, Watanabe K, Negoro T, et al. Infantile spasms: etiological factors, clinical aspects and long-term prognosis in 200 cases. *Eur J Pediatr* 1981; **135**: 239–44.
- 13 Riikonen R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. *Neuropediatrics* 1982; **13**: 14–23.
- 14 Hrachovy RA, Frost JD, Kellaway P. Sleep characteristics in infantile spasms. *Neurology* 1981; **31**: 688–94.
- 15 Commission on Pediatric Epilepsy of the International League Against Epilepsy. Workshop on infantile spasms. *Epilepsia* 1992; **33**: 195.
- 16 Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; **30**: 389–99.

- 17 Dulac O, Plouin P, Jambaque I, Motte J. Spasmes infantiles epileptiques benins. *Revue d'Electroencephalographie et Neurophysiologie Clinique* 1986; 16: 371-82.
- 18 Chugani HT, Shewmon DA, Sankar R, Chen BC, Phelps ME. Infantile spasms: II. Lenticular nuclei and brain stem activation on positron emission tomography. *Ann Neurol* 1992; 31: 212-9.
- 19 Dulac O. Convulsions et epilepsies du nouveau ne et du nourrisson. In: Arthuis M, Pinsard N, Ponsot G, eds. *Neurologie pediatrique, medecine-sciences*. Paris: Flammarion, 1990: 163-95.
- 20 Melchior JC. Infantile spasms and early immunisation against whooping cough. Danish study from 1970 to 1975. *Arch Dis Child* 1977; 52: 134-7.
- 21 Bellman MH, Ross EM, Miller DL. Infantile spasms and pertussis immunisation. *Lancet* 1983; i: 1031-4.
- 22 Elian M, McKenzie S. Infantile spasm - enigma of the genes. *Seizure* 1992; 1 (suppl A): P9/06.
- 23 Adams RD, Victor M. Normal development and deviations in development of the nervous system. In: Adams RD, Victor M, eds. *Principles of neurology*. 4th Ed. New York: McGraw-Hill, 1989: 457-61.
- 24 Huttenlocher PR. Dendritic development of neocortex of children with mental defect and infantile spasms. *Neurology* 1974; 24: 203-10.
- 25 Neville BGR. The origin of infantile spasms: evidence from a case of hydranencephaly. *Dev Med Child Neurol* 1972; 14: 644-7.
- 26 Snead OC. Treatment of infantile spasms. *Pediatr Neurol* 1990; 6: 147-50.
- 27 Matsumoto A, Watanabe K, Negoro T, et al. Prognostic factors of infantile spasms from the etiological viewpoint. *Brain Dev* 1981; 3: 361-4.
- 28 Hrachovy R, Glaze DG, Frost JD. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. *Epilepsia* 1991; 32: 212-4.
- 29 Dreifuss F, Farwell J, Holmes G, et al. Infantile spasms; comparative trial of nitrazepam and corticotrophin. *Arch Neurol* 1986; 43: 1107-10.
- 30 Siemes H, Shohr HL, Michael Th, Nau H. Therapy of infantile spasms with valproate; results of a prospective study. *Epilepsia* 1988; 29: 553-60.
- 31 Prats JM, Garaizar C, Rua MJ, Garcia-Nieto ML, Madoz P. Infantile spasms treated with high doses of sodium valproate; initial response and follow-up. *Dev Med Child Neurol* 1991; 33: 617-25.
- 32 Hrachovy RA, Frost JD, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. *J Pediatr* 1983; 103: 641-5.
- 33 Blennow G, Starck L. High dose B₆ treatment in infantile spasms. *Neuropediatrics* 1986; 17: 7-10.
- 34 Echenne B, Dulac O, Parayre-Chanez MJ, et al. Treatment of infantile spasms with intravenous gamma-globulins. *Brain Dev* 1991; 13: 313-9.
- 35 Tatzner E, Groh C, Muller R, Lischka A. Carbamazepine and benzodiazepines in combination - a possibility to improve the efficacy of treatment of patients with 'intractable' infantile spasms? *Brain Dev* 1987; 9: 415-7.
- 36 Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. *J Child Neurol* 1991; 6 (suppl 2): S52-9.
- 37 Appleton RE, Montiel-Viesca F. Vigabatrin in infantile spasms; why add-on? *Lancet* 1993; 341: 962.
- 38 Sorel L, Dusaucy-Bauloye A. A propos de 21 cas d'hypsarrhythmia de Gibbs; son traitement spectaculaire par l'ACTH. *Acta Neurologica Psychiatrica Belgica* 1958; 58: 130-1.
- 39 Bobele GB, Bodensteiner JB. The treatment of infantile spasms by child neurologists in the United States: a 1991 survey. *Ann Neurol* 1991; 3: A461.
- 40 Baram TZ. Pathophysiology of massive infantile spasms: perspective on the putative role of the brain adrenal axis. *Ann Neurol* 1993; 33: 231-6.
- 41 Singer WD, Rabe EF, Haller JS. The effect of ACTH therapy upon infantile spasms. *J Pediatr* 1980; 96: 485-9.
- 42 Glaze DG, Hrachovy RA, Frost JD, Kellaway P, Zion TE. Prospective study of outcome of infants with infantile spasms treated during controlled studies of ACTH and prednisone. *J Pediatr* 1988; 112: 389-96.
- 43 Parekh HU, Dunn DW. Infantile spasms. *Ann Neurol* 1990; 28: A473-4.
- 44 Lopes I, Troncoso L, Troncoso M, Japaz O, Novoa F. Infantile spasms: brief and intermittent treatment with synthetic ACTH. *Pediatr Neurol* 1992; 8: A391.
- 45 Willig RP, Lagenstein I. Use of ACTH fragments in children with infantile spasms. *Neuropediatrics* 1982; 13: 55-8.
- 46 Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980; 55: 664-72.
- 47 Ring HA, Trimble MA, Costa DC, George MS, Verhoeff P, Ell PJ. Effect of vigabatrin on striatal dopamine receptors: evidence in humans for interactions of GABA and dopamine systems. *J Neurol Neurosurg Psychiatry* 1992; 55: 758-61.
- 48 Shields DW, Shewmon DA, Chugani HT, Peacock WJ. Treatment of infantile spasms: medical or surgical? *Epilepsia* 1992; 33 (suppl 4): S26-31.