

Epileptic spasms – 175 years on: Trying to teach an old dog new tricks.

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Abstract

Infantile spasms, first described by Dr West in 1841, has undergone extensive investigation to understand the pathogenesis, aetiologies, optimal intervention and most likely prognosis for the affected child. The terminology has recently evolved such that the preferred term for the condition is now “epileptic spasms” in recognition of the fact that cases can present outside infancy. The aetiologies are diverse and can be structural, genetic, metabolic or acquired. Increasing numbers of presumed causative genetic mutations are now being identified. The condition is an epileptic encephalopathy such that without adequate control of the clinical seizures and correction of the abnormal EEG, ongoing neurological damage occurs. In some cases neuroregression is inevitable despite intervention. First-line treatments are either hormonal therapies, adrenocorticotrophic hormone or prednisolone, or vigabatrin. In the sub-group of patients with tuberous sclerosis complex, vigabatrin is the preferred treatment. High dose prednisolone may be a more viable option in resource limited settings. Recent research has suggested that combining hormonal therapies with vigabatrin will result in more patients achieving spasm cessation. Despite extensive study, the pathogenic mechanisms remain an area of debate and in need of further exploration. The enigma, however, may be explained as the role of resting state and dysfunctional brain networks are elucidated further.

Key words: infantile spasms, late-onset epileptic spasms, ACTH, oral corticosteroids, prednisolone, vigabatrin

The history of Infantile spasms

Infantile spasms (IS) were first described by Dr West in 1841 when he wrote a letter to the Lancet about his own child's clinical events. His son was healthy until 4 months of age when Dr West noticed that he had "slight bobbings of the head forward" which increased in frequency and intensity with time. He reported that whilst he was a "fine grown child" he lacked "intellectual vivacity" and "power of moving his limbs, of a child of his age".(West, 1841)Over 100 years later, in 1954, Gibbs *et al* published their description on hypsarrhythmia in Pediatrics.(Gibbs et al., 1954). This electroencephalographic finding in IS was described as chaotic and disorganized background activity with asynchronized large amplitude slow waves mixed with single focal, multifocal spikes and slow wave followed by attenuation. In 1958, reported that adrenocorticotrophic hormone (ACTH) controlled the spasms in a number of cases.(SOREL and DUSAUCY-BAULOYE, 1958) Previously there were no known effective treatments for the condition. After this report numerous other studies have confirmed the efficacy of ACTH, corticosteroids and vigabatrin. Since then the semiology of infantile spasms, both clinically and electrically, has been extensively reviewed and the term West Syndrome established, consisting of the triad of spasms, intellectual disability and hypsarrhythmia.

Infancy is the highest risk period for epileptic seizures and epileptic spasms are the most prevalent infantile epilepsy type.(Wilmshurst et al., 2015) The morbidity from this type of epilepsy is often significant.

As the condition was studied more it became evident that cortical malformations and genetic disorders were important causes of IS.

A large single centre study of 150 infants with infantile spasms, assessed their long term outcome.(Jeavons et al., 1973) The subsequent prognosis of this group was that 22% died,16% attended normal school and the remainder required school learning support or day-care, with 34% severely affected. Fifty-five percent went on to develop other seizure types and 47% had abnormal neurological signs. Overall they illustrated the legacy of neurodisability associated with the majority of children who had infantile spasms.(Jeavons et al., 1973) This was further supported by the findings of Riikonen *et al* in the epidemiological study of patients with IS in Finland.(Riikonen, 1982) Poor prognosis related to early onset, long duration of spasms and presence of developmental delay at onset. But the infants with "cryptogenic aetiology" had a better prognosis.(Jeavons et al., 1973) (Riikonen, 1982)

Definitions

The West Delphi study group, following input from 31 clinicians in 15 countries, devised criteria for diagnosing infantile spasms based on clinical signs.(Lux and Osborne, 2004)The group concluded that the primary clinical outcome, namely cessation of spasms, should be defined by the absence of witnessed spasms from within 14 days of commencement of treatment, and 28 consecutive days, or more, from the last witnessed spasm. Primary electroclinical outcome was defined by cessation of

spasms with resolution of hypsarrhythmia. The group defined West syndrome as a subset of the syndrome of infantile spasms. They supported the idea that an infantile spasms single-spasm variant should be recognized. The report provides a standard for reporting modifying and atypical features of hypsarrhythmia. It also suggests a minimal set of baseline characteristics and outcomes that should be reported in trials of patients with infantile spasms, and suggests a standard definition of relapse. The group were unable to reach consensus on a definition of hypsarrhythmia.

Clearly access to electroencephalography (EEG) is important in the diagnosis and management of infantile spasms. But access to EEG in resource limited settings is a major challenge, as in most settings the tool is not available, or is limited to psychiatric or adult neurology services.(Wilmshurst et al., 2013) Pre-symptomatic monitoring with regular EEGs is recommended in high-risk populations such as infants with TSC.(Curatolo et al., 2012) Also for assessment of subtle spasms, prolonged EEG monitoring has been supported with video-EEG studies between 8-24 hours in duration.(Wilmshurst et al., 2015) These logical recommendations are also not viable in most resource limited settings.

The condition of late-onset infantile spasms is an accepted entity, to the extent that the preferred term is no longer infantile spasms but now referred to as late-onset epileptic spasms.(Ronzano et al., 2015; Ishikawa et al., 2014) This condition is often associated with focal cortical dysplasia type 1.(Metsähonkala et al., 2015) Patients may have severe mental impairment but seizures can be remedial to surgical interventions. These late-onset epileptic spasms (ES) are distinct from West syndrome and Lennox-Gastaut syndrome. In a study of 8 symptomatic patients with late-onset ES(Ishikawa et al., 2014) all patients had neurological deterioration in addition to multiple seizure types, which were intractable in seven. Interictal EEG showed no typical hypsarrhythmia. The predominant tonic seizures were ES, spasms followed by tonic seizures (SFT), and tonic seizures. The clinical characteristics were reported to be consistent with infantile epileptic encephalopathy with late-onset spasms in those infants with core seizure types of ES, SFT, and tonic seizures, ES beyond the age of 1 year, and neurological deterioration.

It is through the recognition that infantile spasms are not restricted to the infantile period that the terminology has moved away from this to re-termining the condition “epileptic spasms” (ES).(Berg et al., 2010)

Epidemiology

Epileptic spasm is an age related disorder. It is the most common epileptic syndrome in infancy. The incidence of IS has been estimated to range 2-5/10,000 newborns. Studies from high income countries showed wide range incidence rate (0.05 -0.6/ 1000 liveborns) higher reported incidence were reported from the higher geographic latitudes; Sweden, Finland and Denmark and lowest incidence in United States of America, Britain and Korea. It is not clear if this difference were due to environmental factors or specific genetic predisposition. The age specific prevalence is around 1-2/10000 children by age of 10 years. Like incidence the highest prevalence values also corresponds

to high geographical latitude.(Cowan and Hudson, 1991; Riikonen, 2001; Pavone et al., 2014)There are scant report from sub-Saharan Africa on the incidence or prevalence of ES. In the review of the epidemiology of epilepsy in resource limited countries Senanayaka and Roman did not include epileptic spasm among the seizure types reviewed,(Senanayake and Román, 1993) while in a survey of childhood epilepsy in rural Uganda, though none of the 440 children reviewed then had ES, 7 of them had previous history suggestive of ES.(Duggan, 2010)

The age of onset is reported to vary from the first week of life up to 3 years. The peak is between 4 and 7 months, age of onset is within one year in 94% of cases. Almost all cases occur within 3 years of age. However, rare cases of epileptic spasm with onset at up to 14 years of age are reported, hence the new preferred term of epileptic spasm which was first suggested in the 1991 workshop of the ILAE commission on paediatric epilepsy.(International and Epilepsy., 1992)

Whilst studies suggest a slight male predominance in the prevalence of ES in the average ratio of 6:4, this finding is not consistent. The reason for this differences is not clear, Brna *et al* suggested that the observed male predominance in some studies simply reflects the predominance in males in the referring population.(Brna et al., 2001) An alternate explanation is the increased complication rate in predisposing conditions such as neonatal hypoglycaemia and HIE reported to occur in male infants.(Tundidor et al., 2012)

Aetiologies

A study of 269 infants with ES in a national childhood encephalopathy study, found that 34% had antecedent factors which may have caused the spasms, the commonest of these were perinatal hypoxia in 38 cases and TSC in 16 cases.(Bellman et al., 1983) This case control analysis showed no significant association between ES and pertussis immunisation in the 28 days before onset. There was some clustering of cases immunised with either diphtheria, tetanus and pertussis (DTP) or DT vaccines in the 7 days before onset.This study was important to emphasise and support that vaccinations did not cause ES but could trigger their onset in infants in whom the disorder was predestined to develop.

A further study of 207 infants with epileptic spasms found that, 127 (61%) had a proven aetiology, 68 (33%) had no identified aetiology, and 12 (6%) were not fully investigated.(Osborne et al., 2010). Aetiologies were prenatal in 63, perinatal in 38, postnatal in 8, and 18 had other causes. The most common aetiologies were: hypoxic-ischemic encephalopathy (HIE) n=21 (10%), chromosomal n=16 (8%), malformations n=16 (8%), stroke n=16 (8%), tuberous sclerosis complex (TSC) n=15 (7%), and periventricular leukomalacia or hemorrhage n=11 (5%). The remaining 32 aetiologies were all individually uncommon.

The National Infantile Spasms Consortium in North America prospectively evaluated the aetiology of new-onset epileptic spasms and evaluated the yield of genetic and metabolic investigations in those

without obvious cause after initial clinical evaluation and magnetic resonance imaging (MRI). (Wirrell et al., 2015) Twenty-one United States paediatric epilepsy centers prospectively enrolled infants with newly diagnosed West syndrome in a central database. A total of 251 infants were enrolled (53% male). A cause was identified in 161 (64.4%) of 250 cases (genetic, 14.4%; genetic-structural, 10.0%; structural-congenital, 10.8%; structural-acquired, 22.4%; metabolic, 4.8%; and infectious, 2.0%). An obvious cause was found after initial clinical assessment (history and physical examination) and/or MRI in 138 of 161, whereas further genetic and metabolic studies were revealing in another 23 cases. Of 112 subjects without an obvious cause after initial evaluation and MRI, 81 (72.3%) had undergone genetic testing, which showed a causal abnormality in 23.5% and a variant of unknown significance in 14.8%. Although metabolic studies were done in the majority, these revealed an aetiology in only five cases (4.5%). The group concluded that the clinical evaluation and MRI provided a specific diagnosis in 55% of children presenting with West syndrome. They recommended a cost-effective workup for those without obvious cause, after initial clinical evaluation and MRI, that should include an array comparative genomic hybridization (aCGH) followed by an epilepsy gene panel if the microarray is not definitive, as well as serum lactate, serum amino acids, and urine organic acids.

Genetics causes are increasingly recognised as a cause of epileptic spasms. Genetic causes can either be disorders of genomic imbalance (e.g. Down's syndrome, Palister-Killian syndrome, Williams syndrome or Miller-Dieker syndrome) or single gene disorders such as mutations in *CDKL5*, *STXBP1*, or *ARX*. Recent discoveries of responsible gene mutations, such as in *GRIN2B* that codes for the *NR2B* sub-unit of the N-methyl-D-aspartate (NMDA) receptor and results in a gain of function, raise the possibility of novel treatments that may be directed at the molecular pathology e.g. NMDA receptor antagonists. (Lemke et al., 2014) A recent study of 73 infants with ES and no clear aetiology underwent array-CGH and molecular analysis of 5 genes (*CDKL5*, *STXBP1*, *KCNQ2*, *GRIN2A* and *MAGI2*). (Boutry-Kryza et al., 2015) A disease-causing mutation or CNV (Copy Number Variation) was identified in 15% of the patients. Which included 6 point mutations found in *CDKL5* (n = 3) and *STXBP1* (n = 3), 3 microdeletions (10 Mb in 2q24.3, 3.2 Mb in 5q14.3 including the region upstream to *MEF2C*, and 256 kb in 9q34 disrupting *EHMT1*), and 2 microduplications (671 kb in 2q24.3 encompassing *SCN2A*, and 11.93 Mb in Xq28). In addition, 3 CNVs as potential risk factors, including one 16p12.1 deletion, one intronic deletion of the *NEDD4* gene, and one intronic deletion of *CALN1* gene.

Metabolic aetiologies are rare but also recognised. Pyridoxine dependency, biotinidase deficiency, PEHO syndrome, mitochondrial disorders, molybdenum co-factor deficiency and non-ketotic hyperglycaemia have all been described. (Alrifai et al., 2014)

Pathogenesis

The underlying pathogenesis of ES is not fully understood. The condition is proposed to be a derangement of a network, or a system epilepsy. The mechanism for the associated encephalopathy is still not fully elucidated. It is hypothesised that the encephalopathy is a reflection of the background slowing and disruption in the normal brain rhythms due to a disturbance in brain networks. The infant

is especially vulnerable to the development of epileptic spasms based on their stage of brain maturation and the time window that this places them in. Hence a wide range of aetiologies have the capacity of leading to the same outcome, namely ES and often West syndrome, they have the equivalent mechanism of flipping a switch (which may have been predestined in a vulnerable child or directly operational in instigating the ripple effect of damage). (Pellock et al., 2010) A common mechanism involved in the diverse cases of ES is proposed to be due to brainstem pathology. (Hrachovy and Frost, 1989) An infant with hydrancephaly was able to generate ES which was clinically identical to that seen in infants with intact nervous systems and supported that the brainstem is able to generate spasms. (Neville, 1972) Further supporting data was evident from other studies assessing MRI and evoked potential results, and when reviewing the progress of neonates who suffered hypoxic-ischaemic injuries to their subcortical and brainstem regions and subsequently developed ES. (Miyazaki et al., 1993; Gano et al., 2013) Further concepts arose that spasms could be triggered by an interaction between the cortical grey and subcortical structures. Once activated the subcortical, brainstem or both could become generators of epileptic spasms. (Chugani et al., 1990; Guggenheim et al., 2008) These findings support the idea that the pathogenesis is more complex and more likely related to widely disrupted networks at a particular stage of development and that this process is implicit in the associated encephalopathy. The encephalopathy precedes the development of the spasms. (Philippi et al., 2008) The EEG background pattern for children with ES and the other epileptic encephalopathies is typically extremely disrupted, independent of the ictal events, electrodecrements and periods of discontinuity which occur. (Nordli, 2014) Extending on these findings, the disruption in the resting state networks of the brain by chaotic brain activity could be responsible for the global cognitive dysfunction seen in children with epileptic encephalopathies, especially those with ES. (Nordli, 2013)

Clinical Manifestation

Semiology

Epileptic Spasms are brief and abrupt contractions followed by less intense and sustained tonic phase lasting up to 1 -2 seconds which involves the muscles of the neck, trunk, upper and lower limbs. They are more prolonged than a myoclonic jerk but less sustained than a tonic seizure. The spasms may be flexor, extensor or mixed. The flexure spasms is the most common, there is however wide individual variability in both the intensity and type of jerks. (Pavone et al., 2014) The spasm could be symmetrical or asymmetrical, focal, multifocal or generalized. Children with underlying cortical damage may have pre-existing focal neurological signs e.g. hemiparesis that inevitably mean the spasms will not be symmetrical. Infact on account of the uncertainty in the true characteristics of ES, in the new ILAE classification of epileptic seizures ES is not classified either as focal or generalized. (Berg et al., 2010) The clinical significance of subtle spasm with features such as yawning, gasping, isolated eye movement and transient focal motor activities which has been reported is unknown but they occur in the context of classical EEG pattern of IS – hypsarrhythmia. (Lux AL & Osborne JP (2004)

Clinical phenomena that may be associated with the motor spasm before, during or after the attack include cyanosis, pallor, eye deviation and or change in respiratory pattern. Cry or scream may precede or follow the ictal phase. Often infants will be disturbed or upset by the spasms.

Spasms usually occur in clusters; this was observed by West in his original description. Approximately 80% of spasms occur in clusters and 88% of patients report clustering phenomenon. Studies have shown that there is little diurnal variation in frequency of spasm/cluster over a 24 hour period. However, spasms do not occur in sleep but occur most frequently on awakening or just before sleep.

Electroencephalographic findings

The classic hypsarrhythmia seen in patients with IS is an EEG pattern of a poorly organized, high amplitude (500– 1000 μ V), slow background, with accompanying multifocal epileptiform discharges, seen interictally, with generalized electrodecrement seen ictally during the spasms. It is however not present in all cases of IS and variation or modification of hypsarrhythmia is reported. . For an excellent review of the pattern and implication of these variants of hypsarrhythmia readers are referred to Hrachovy and Frost. (Hrachovy and Frost, 2003)

There are children with IS whose inter-ictal EEG does not show hypsarrhythmia or any of its variants. Caraballo *et al* followed up 16 such cases and observed focal spikes in seven cases, bilateral spikes and spike and waves in five patients, multifocal spikes in two and normal inter-ictal EEG in two patients.(Caraballo *et al.*, 2011)

Benign non-epileptic IS has been reported by some workers and these children have an excellent prognosis with a normal EEG. According to current knowledge a normal EEG excludes the diagnosis of IS.(Dravet *et al.*, 1986)

Management

With regards to interventions, the first report of corticoadrenal hormones used therapeutically in epilepsy was published by McQuarrie*et al.*(McQuarrie *et al.*, 1942)McQuarrie observed (1931) seizures induced in epileptic patients by increasing water intake and giving ADH. Deoxycortisone was proposed to cause opposite effects and therefore could have antiepileptic properties. They administered the intervention to one patient, with complete resolution of seizures. Further studies specific to the role of corticosteroids in the treatment of ES, added to the wealth of data relating to this condition and the combined findings led to recommendations from the American Academy of Neurology, as well as the Cochrane database, for hormonal therapies to be the optimal intervention.(Go *et al.*, 2012; Hancock *et al.*, 2013)

Data from The National Infantile Spasms Consortium of North America supported the need to follow accepted standardized protocols namely adrenocorticotrophic hormone (ACTH), oral corticosteroids or vigabatrin (VGB).(Knupp *et al.*, 2016) The paper stated that more favourable responses occurred in

the ACTH treated group but this was a prospective case series and not a scientific clinical trial and therefore the results need to be viewed with some caution because of the possibility of bias .

The role of vigabatrin was reported in a study in which 192 out of 250 infants with classic ES were retrospectively reviewed.(Aicardi et al., 1996) Median follow-up time was 7.6months (range 0.5-28.6months). Initial suppression of ES occurred in 131 (68%) infants. In the group with TSC this was 27/28 (96%).In infants under 3 months of age at the time of the spasms onset resolution occurred in 18/20 (90%). Response time was 4 days and mean dose was 99mg/kg/day. Comparison of vigabatrin versus hydrocortisone in a prospective randomised multicentre study compared responses in 22 patients with TSC.(Chiron et al., 1997) The study supported the superior efficacy and tolerability of VGB in infants with TSC and ES when compared with hydrocortisone. However, it should be noted that hydrocortisone is rarely used elsewhere in the treatment of IS. Another study of 42 patients found no significant difference between vigabatrin and ACTH. In the VGB group 11/23 became spasm free with more efficacy seen for the patients with TSC and or malformations, with 13% reporting side effects.(Vigevano and Cilio, 1997) 14/19 administered ACTH responded with earlier resolution on EEG and side effects reported by 37%.

Concern relating to VGB and visual field defects has affected confidence in prescribing the product.(Vanhatalo et al., 2002) A study of 91 children aged between 5.6 and 17.9 years, found visual field constriction in 17/91 (which was not statistically significant). But significant correlation was found with development of constriction in children who were treated for longer periods. The constricted group were treated for 46.1 months compared to the normal visual field (VF) group who were treated for 33.5 months. Also the cumulative dose was a statistically significant positive risk indicator.

The multicentre, randomised controlled trial, the United Kingdom Infantile Spasms Study (UKISS) compared prednisolone or tetracosactide versus VGB in the treatment of IS.(Lux et al., 2004) In this study children with TSC were excluded. The primary clinical outcome was the proportion with no spasms at days 13 and 14. This was found in 73% of the hormonal group and 54% of the VGB group which was statistically significant. Adverse events were reported in 55% of the hormonal group and 54% of the VGB group. Follow up data at 14 months based on the absence of spasms at final clinical assessment found that this was the case for 41/55 of the hormonal group (75%) compared to 39/51 of the VGB group (76%).(Lux et al., 2005) The mean VABS score for the hormone group was 78.6 [SD 16.8] and the VGB group was 77.5 [SD 12.7]; also not significant. However, there was a significant aetiology-treatment interaction with respect to developmental outcome with hormonal therapies being associated with a significantly better developmental outcome than vigabatrin in those children with no proven aetiology for their spasms.

In resource limited settings access to ACTH or vigabatrin may not be viable. Indeed even in many parts of the US the cost of ACTH often precludes its use as therapy. Data is evolving supportive of high dose prednisolone (8mg/kg/day, or 40- 60mg per day, for 2 weeks of therapy followed by a 2 week taper) with equivalent responses to those seen with ACTH.(Kossoff et al., 2009; Hussain et al., 2014)

The ketogenic diet has been proposed as an alternate intervention for infants with epileptic spasms but studies have provided inconsistent results.(Eun et al., 2006; Hong et al., 2010; Kang et al., 2011; Kayyali et al., 2014; Kossoff et al., 2008; Lee et al., 2013; Pires et al., 2013; Hussain et al., 2016) Most studies introduce the intervention after failure of standard therapy. The ideal study is yet to be performed to clarify if the KD is a viable option in the management of ES.

Precision medicine is a concept which, whilst relatively novel, may have a role for isolated patients with IS. An example could be in the setting of patients with IS related to *KCNT1* mutations.(Ohba et al., 2015) Effective response to quinidine is reported in one case study.(Fukuoka et al., 2016) Some caution is needed however as there is variable response for patients with *KCNT1* mutations and early onset epileptic encephalopathies.(Chong et al., 2016)

Outcome

Focusing on the developmental outcome, no difference in developmental outcome was found between the two treatment groups (hormonal treatment versus VBG) for all infants.(Darke et al., 2010) In the subgroup of infants with no identified aetiology, hormonal treatments had a significantly higher composite VABS scores than those allocated vigabatrin when measured both at 14 months and at 4 years.

The study was extended into The International Collaborative Infantile Spasms Study (ICISS), which measured cessation of spasms (Day 14 – 42), cessation of spasms and resolution of hypsarrhythmia (electro-clinical outcome), development at 18 months and 3.5 years. The primary clinical outcome of cessation of seizures between Day 14 and 42 was seen in 108 (56.6%) out of 191 allocated hormonal treatment compared to 133 (71.9%) out of 185 allocated combination therapy (VGB and hormonal therapy). Difference in response was 15.3% (95% CI = 5.4% to 25.2%) $\chi^2 = 9.6$, $p = 0.002$. The median response time in responders for those on combination therapy was 2 days (IQR 2-4) compared to a median response time of 4 days (IQR 3-6) for those responding to hormonal therapy alone (Wilcoxon ranksum $z=6.04$ $p < 0.0001$). The implication being that optimal management would be through combination of hormonal as well as VBG treatment.

Another key factor associated with developmental outcome is the “lead time to treatment” i.e.the time from seizure onset to initiation of treatment.(O’Callaghan et al., 2011) In this study that looked at participants in UKISS (ref Lux et al.) lead-time to treatment was categorised as 7 days or less, 8 to 14 days, 15 days to 1 month, 1 to 2 months and greater than two months. The study showed that the earlier the intervention the better, each increase in category of lead time duration was associated with a 3.9 (95% CI 0.4 to 7.3, $p = 0.014$) decrease in VABS score.

Additional influences on outcome relate to the impact of the underlying aetiology. In general symptomatic cases do worse than infants with cryptogenic causes.(Riikonen, 2001) Further, certain genetic mutations can have specific outcomes, such as *ARX* mutations which impact on autistic outcome.(Turner et al., 2002) The prompt response to treatment and a short duration of hypsarrhythmia is also an indicator.(Renner-Primec et al., 2006) This has also been reported in patients

with infantile spasms and TSC (Jambaqué et al., 2000) as well as those with IS and Trisomy 21 (Eisermann et al., 2003).

Epilepsy surgery

There is a subset of children with ES who may be suitable for epilepsy surgery. Focal lesions in Infantile Spasms are supported by findings in EEG recordings in 110/149 in one study (Riikonen, 1982) and in 28/67 in another, (Kramer et al., 1997). Also on neuroimaging (CT/MRI) in 17/37 infants, (Shields et al., 1992) and following positron emission tomography (PET) in 5/13 infants (Chugani et al., 1993) and 30/97 infants (Chugani and Conti, 1996). Epilepsy surgery was undertaken in 23 children between 1-10 months of age (mean 9.5 months), based on supporting data from PET and EEG which was lateralised/localised in all. (Chugani et al., 1993) Fifteen children underwent cortical resection and 8 hemispherectomy. At follow-up between 4-67 months, 15 were seizure free, 4 had between 75-90% seizure freedom and 4 continued to have seizures.

With regards to developmental outcome, a study of 24 children with IS (15 girls) who underwent epilepsy surgery found a significant increase in developmental level at 2 years postsurgery compared with presurgical levels. (Asarnow et al., 1997) Younger age at operation correlates with a better outcome. (Riikonen, 1982; Koo et al., 1993; Favatà et al., 1987; Glaze et al., 1988) The longer the period of seizure duration before surgical intervention the lower Vineland DQ. (Jonas et al., 2005) This is further supported by the study by Loddenkemper *et al* which found that better developmental outcome was found in the early surgical intervention group. (Loddenkemper et al., 2007)

Summary / Overall

Epileptic spasms remain in many ways a conundrum, the ideal intervention is still unravelling, as well as how to best to screen patients with the intent for optimal care, and certainly with regards to the genetic causative mutations, the list could be exhaustive. As the vast range of genetics causes for ES evolve, it will be important to structure cost effective screening tools and to assess where the results will alter management i.e. precision medicine. However in most settings early recognition and intervention remain the priority of care to aim for optimal outcome for the infant.

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