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The Underlying Aetiology of Infantile Spasms (West Syndrome): Information from the International Collaborative Infantile Spasms Study (ICISS)

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Conflict of Interest:

During the course of this study, FJKO'C, SWE, EH, ALL and JPO have received a payment from Marathon Pharmaceuticals for intellectual property. The study sponsor has received a payment from UCB Biopharma for intellectual property. DR received a grant from the Bonner-Bender stiftung. FDA, MCB, ALJ, CRK, ML, MTM, AMM, RWN, MN, RP, BS and CMV declare no competing interests.

Ethical publication statement:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

SUMMARY

Objective: To determine the underlying aetiologies in a contemporary cohort of infants with infantile spasms and to examine response to treatment.

Methods: Identification of the underlying aetiology and response to treatment in 377 infants enrolled in a clinical trial of the treatment of infantile spasms between 2007 and 2014 using a systematic review of history, examination and investigations. They were classified using the paediatric adaptation of ICD 10.

Results: 219 of 377 (58%) had a proven aetiology of whom 128 [58%] responded, 58 of 108 [54%] allocated hormonal treatment and 70 of 111 [63%] combination therapy. Fourteen of 17 (82%, 95% CI 59% to 94%) infants with stroke and infarct responded (compared to 114 of 202 for the rest of the proven aetiology group (56%, 95% CI 48% to 62%, Chi square 4.3, $p=0.037$): the better response remains when treatment allocation and lead time are taken into account (Odds ratio 5.1, 95% CI 1.1 to 23.6, $p=0.037$).

20 of 37 (54%, 95% CI 38% to 70%) infants with Down's syndrome had cessation of spasms compared to 108 out of 182 (59%, 95% CI 52% to 66%, Chi square 0.35, $p=0.55$) for the rest of the proven aetiology group. The lack of a significant difference remains after taking treatment modality and lead-time into account (Odds ratio 0.8, 95% CI 0.4 to 1.7, $p = 0.62$). In Down's infants treatment modality did not appear to affect response: 11 out of 20 (55%) allocated hormonal therapy responded, compared to 9 out of 17 (53%) allocated combination therapy.

Significance: This classification allows easy comparison with other classifications and with our earlier reports. Stroke and infarct has a better outcome than other

aetiologies while Down's syndrome might not respond to the addition of vigabatrin to hormonal treatment.

INTRODUCTION

Infantile spasms, also known as West syndrome, constitutes a severe form of infantile epilepsy that is difficult to treat and is associated with a poor outcome^[1]. The syndrome was the first described epileptic encephalopathy— a condition in which the epileptic activity itself contributes to cognitive and neurological decline^[2-4]. Infantile spasms have an estimated incidence of about 0.43 per 1000 live births and occur predominantly between 3 and 12 months of age with a peak incidence around 6–7 months^[5]. Approximately 60% of cases have a diagnosed neurological disorder – the underlying aetiology - that is considered to predispose the individuals to infantile spasms^[6-8]. To detect an underlying aetiology it is necessary to investigate the antenatal, perinatal and infant's history, to examine the infant and to undertake relevant investigations. Despite this, some infants will have no detectable neurological disorder and there is no explanation as to why they have infantile spasms.

It is also unclear why some individuals with a particular neurological disorder develop infantile spasms while others, with the same disorder, do not. It is for this reason that it is preferable to talk about an underlying aetiology rather than a cause. The underlying aetiology usually carries, independently of the spasms, a risk of developmental impairment which may or may not be severe. As a result, infants with an underlying aetiology have, on average, a worse developmental outcome than the large minority of infants who have no such disorder identified^[9].

We have previously reported on the underlying aetiology of 207 infants in our earlier study, the United Kingdom Infantile Spasms Study (UKISS)^[6] which enrolled infants between June 1999 and the end of 2002. We thought that the more prevalent use of cranial magnetic resonance imaging and the development of diagnostic genetic technologies since 2002 would lead to improved diagnostic detection today and therefore we determined to see what new information was available during our next study, the International Collaborative Infantile Spasms Study (ICISS) which enrolled from 2007 to 2014^[10]. We also report the response to treatment for each identified aetiology, since this might help identify specific aetiologies that have a particular response to treatment.

METHODS

377 infants were enrolled between March 2007 and May 2014 into a randomized controlled trial comparing hormonal treatment (either prednisolone or tetracosactide depot) alone to hormonal treatment with vigabatrin. Full details have already been published^[10]. Minimum treatments were oral prednisolone 40mg per day, intramuscular Tetracosactide depot 0.5mg (40iu) on alternate days and oral vigabatrin 100mg per day. The hormonal treatments were given for 14 days followed by a reducing dose of oral prednisolone for 15 days while vigabatrin was continued for 3 months before reducing over the next month. A response to treatment in ICISS was defined as no witnessed spasms on and between days 14-42 from study entry^[11]. In order to allow direct comparison with the results from UKISS, we also present, in a web appendix, the response to treatment in the ICISS cohort

using the definition applied in UKISS – no witnessed spasms on days 13 and 14 from study entry.

As part of the trial, investigators had to report on the underlying aetiology after investigations they considered appropriate, including history (including antenatal, perinatal and postnatal history), examination, fundoscopy, metabolic screen, chromosome analysis and cranial imaging. Report forms were scrutinized by two of the steering group (JPO and FJKO'C) and where considered necessary, additional information was requested. All report forms until age 18 months were scrutinized for aetiological information. Infants were classified as aetiology not known where key information was missing, such as history, examination or cranial scan. A metabolic screen was requested but the result was not chased if an aetiology was already established. An independent review of the cranial MRI scans by a paediatric neuro-radiologist was also requested when considered necessary (ML). The results were used to classify the underlying aetiology using the paediatric adaptation of the International Classification of Diseases 10th edition (ICD 10)^[12]. This adaptation also classifies aetiology by the timing of the onset of the disorder into the categories prenatal, perinatal, postnatal and “other (or not known)” where key information was missing. Diagnoses made using DNA techniques we have classified under chromosomal since no separate DNA category was available. Classification was performed by two investigators (FJKOC and JPO) independently and discrepancies were re-evaluated and a consensus decision made. Before starting the ICISS trial, it was suggested to us in a personal communication that infants with IS secondary to stroke responded particularly well to treatment. We proposed to report this group

in detail. We have also looked at the infants with Down's syndrome following a comment by one reviewer.

Statistical Analysis

The analyses were done by intention to treat. Chi square tests were used for simple comparisons of proportions. Logistic regression was used for multiple multivariable analyses when the primary outcome was binary (eg response to treatment). T tests or Willcoxon rank sum test, depending on normality of distribution, were used for comparison of continuous data. The primary explanatory variable of interest was the effect of treatment but we also examined the effect of lead time, aetiology and age as appropriate. The analyses were undertaken by FJKO'C.

RESULTS

377 infants were enrolled into ICISS and we have results on aetiology in 376 since one case (0.3%) was withdrawn before investigations were complete and was classified as aetiology not known. 157 (42%) had no identified aetiology and 219 (58%) had a proven aetiology of whom 128 responded, 58 of 108 (54%) allocated hormonal treatment and 70 of 111 (63%) allocated combination therapy. Table 1 shows a summary of numbers and response by prenatal, perinatal, postnatal and other categories. Details of specific diseases and their response to treatment is given in the following tables by prenatal, non chromosomal (table 2), prenatal chromosomal (table 3), perinatal (table 4), postnatal (table 5) and other (table 6).

The tables also show the subgroups used in the paediatric adaptation of ICD 10. There were no disagreements in the specific disease classifications by the two individuals involved but there were initially nine disagreements over the likely timing of the disorder. These were all satisfactorily resolved.

Fourteen of 17 (82%, 95% CI 59% to 94%) infants with stroke and infarct responded compared to 114 out of 202 for the rest of the proven aetiology group as a whole (56%, 95% CI 48% to 62%: Chi square 4.3, $p=0.037$). The better response for the stroke group (Table 6) remains when treatment allocation and lead time are taken into account (Odds ratio 5.1, 95% CI 1.1 to 23.6, $p=0.037$).

20 of 37 (54%, 95% CI 38% to 70%) infants with Down's syndrome had cessation of spasms compared to 108 out of 182 (59%, 95% CI 52% to 66%, Chi square 0.35, $p=0.55$) infants in the rest of the proven aetiology group. The lack of a significant difference in response between the two groups remains after taking treatment and lead-time into account (Odds ratio 0.8, 95% CI 0.4 to 1.7, $p = 0.62$, see Table 7).

There was no significant difference in response in the Downs syndrome children according to their treatment modality: 11 out of 20 (55%) allocated to hormonal therapy responded, compared to 9 out of 17 (53%) allocated to combination therapy. We noted that the Down's infants were older (age at enrolment) than the rest of the proven aetiology group (mean age 249 compared to 219 days, Wilcoxon rank-sum $z=-2.192$, $p=0.028$).

DISCUSSION

Classification of aetiologies allows us to look at the presumed causes of illness and how this may change over time. It also enables the study of outcomes for specific patient groups. In this paper we were interested to see if the outcome of spasms differed according to underlying aetiology. We used the paediatric adaptation of ICD 10 to classify aetiologies and this facilitated comparison with the earlier UKISS study that had also used ICD 10. There are some classifications that no longer seem appropriate to us, but we have continued to use the classification as originally suggested. For example, a number of metabolic diseases are classified in the paediatric adaptation of ICD 10 as postnatal aetiologies when it seems reasonable to suggest that they would have caused neurological damage in the prenatal period. Despite such issues, by publishing the full details using ICD 10 it is possible to allow direct comparison with the results from our earlier study. It will also be possible for future researchers to amalgamate our outcomes with theirs, for the meta-analyses of outcomes, including a re-allocation of categories if appropriate. We have however, amalgamated cortical dysplasia and focal cortical dysplasia into one category as the difference is nowadays meaningless.

We do not report infants with developmental impairment at onset of the spasms as having a proven aetiology unless there was a detected underlying aetiology. We believe this to be important since the spasms themselves might have been responsible for the developmental impairment at the time of diagnosis of their

spasms. In this study, no infant was reported as having a CT scan to make an aetiological diagnosis. Cranial MRI was the investigation of choice.

ICISS recruited nearly twice as many infants as the UKISS^[6] aetiological study: 377 versus 207. The 58% in whom an underlying aetiology was identified was similar to the 61% in UKISS while the percentage not fully investigated was lower in the ICISS study (0.3% v 12%). There was no evidence in UKISS, which followed infants not enrolled into the clinical trial as well as those who were, of biased enrollment into the clinical trial related to underlying aetiology (although infants known to have tuberous sclerosis were excluded from both clinical trials) but we have no direct evidence about this from ICISS. The proportion of infants with proven aetiology were the same in UKISS and in ICISS and thus there is no reason to suspect a bias in recruitment related to aetiology.

Eight cortical dysplasias (2%) were identified in ICISS compared to one (0.2%) in UKISS. This probably reflects the increased use of cranial MRI in the later study. However, more detailed investigations that might have identified a focal lesion such as cortical dysplasia, for example FDG-PET, SPECT or MEG, were rarely undertaken and none were reported to us. It should be remembered that children with tuberous sclerosis complex were excluded from the study. In fact five infants with tuberous sclerosis complex were recruited because the diagnosis was made after randomization. These children are not included in the cortical dysplasia category.

Forty whole chromosome disorders, 37 with Down's syndrome, were identified in ICISS (11%) compared to 6 in UKISS (0.3%), five with Down's syndrome. The large increase in infants with Down's syndrome must simply be due to more infants with Down's being enrolled. The number of infants with other genetic conditions has increased from 2% in UKISS to 7% in ICISS, presumably because of better methods of detection including the use of DNA analyses. It is possible that the enthusiasm for investigating in those with no proven aetiology was affected by their response to treatment with those responding and doing well being less likely to have had further investigations such as DNA analyses. In addition more tests will have been available towards the end of the trial in 2014 than at the beginning in 2007. The disparity may be even greater now in 2019 as genetic technologies and access to them have continued to improve.

The absolute numbers of infants with hypoxic ischaemic encephalopathy was lower, 6% in ICISS and 11% in UKISS . Similarly the prevalence of periventricular ischaemia and haemorrhage was lower (3% in ICISS and 6% in UKISS) and for stroke or infarct (5% in ICISS and 8% in UKISS). These differences might possibly reflect improvements in perinatal care. Conversely, the percentage with metabolic disease due to hypoglycaemia were increased, 3% in ICISS compared to 1% in UKISS. This difference, although small, does not suggest that the prevention and management of hypoglycaemia has improved.

In ICISS ^[10], infants with proven aetiology had a worse prognosis than those with no identified aetiology both for cessation of spasms, 58% and 73% respectively

(difference 15%, 95% CI 4.97-25.04, chi 8.9, p=0.003), and for development at 18 months ^[13] as assessed by the Vineland Adaptive Behaviour Scales, VABS 66.8 and 82.5 respectively (66.8[SE 1.0] vs 82.5[1.5], difference 15.7 [95% CI 12.2-19.2], p<0.001). In ICISS, looking at response to treatment by the timing of the initial insult, the numbers in some groups are small which would make comparison unreliable.

Numbers are inevitably small when looking at specific aetiologies. The largest aetiological group were the children with Down's syndrome where the response rate of 54% in ICISS and 55% in UKISS were similar but again here the ICISS definition of response is more stringent but the treatment more successful leading to similar response rates. These response rates are almost identical to the response rate of 59% found in this study (and 60% in UKISS) for pre-natal aetiologies and suggests that infants with Down's syndrome do not have a different response overall to treatment than those with other aetiologies. However, The Down's infants are older on average. This might be due to the later maturation of the brain making the age at which Down's infants are susceptible to infantile spasms older on average. This observation might be useful for determining likely predisposing factors or even causes for infantile spasms. We also noted that Down's infants did not seem to benefit from the addition of vigabatrin to hormonal treatment.

Infants with stroke or infarct did respond better than expected comparing favourably to the response rate for the rest of the proven aetiology group. This suggests that this group of infants does have a better prognosis than other

aetiologies. This conclusion is supported by the results from UKISS which, using a different treatment regime, also found more infants with stroke or infarct to have responded. It may be that these children have a better outcome because their spasms result from a discrete insult to an otherwise normal brain as compared with other children in the proven aetiology group who have a more diffuse injury or a more generalized disorder of brain development.

The aetiological classification used in this paper (and UKISS) is much more precise than the poorly defined and understood traditional categories of symptomatic, cryptogenic and idiopathic that others have rightly criticized ^[14 15]. We have not made any judgements concerning the probability of causality and have simply reported all the underlying aetiologies that were identified including diagnoses, such as arachnoid cysts, that other investigators may have omitted because of their uncertain relationship to the risk of infantile spasms. This approach may, in time, lead to the identification of underlying aetiologies, previously thought to be unimportant, that appear more frequently than expected – thus suggesting a role in infantile spasms.

Since the publication of our original paper on the aetiology of infantile spasms, several authors have published on the subject and some have suggested new and useful aetiological classification systems. Paciorkowski et al., for example, propose a genetic and biologic classification system that is flexible and has much merit^[14]. The recent position paper of the ILAE on the classification of the epilepsies proposes that aetiologies of all the epilepsies should be thought of in terms of six potentially

overlapping categories that should be considered at every step of the diagnostic pathway: structural, genetic, infectious, metabolic, immune and unknown^[4]. The aetiological sub-groups were chosen because of their potential therapeutic consequences. Our data can easily be rearranged to fit these other classification systems but we have chosen to use the system used in our previous paper to facilitate comparison between the two studies.

We conclude that MRI has likely improved the detection of cortical dysplasias. Genetic diagnoses are also more likely to be detected. Our results do not suggest to us that any particular aetiology has a better or worse outcome than any other, except for infants with stroke and infarct. Down's infants might not respond better to the addition of vigabatrin with hormonal treatment but this observation needs to be confirmed. There is also a suggestion that there are reduced proportions of children presenting with infantile spasms secondary to hypoxic ischaemic encephalopathy and this might possibly reflect improvements in prenatal and perinatal care. The death rate in ICISS was very low and the response rate high. We would therefore advocate the use of combination therapy in all aetiological groups including stroke – although for tuberous sclerosis the best treatment has yet to be determined.

Key Points:

1. Multiple underlying aetiologies are found in infants with infantile spasms.
2. Cranial MRI and genetic testing has increased the number of specific aetiologies.
3. Down's syndrome infants might not respond to the addition of vigabatrin.
4. Infants with stroke and infarct have a better than average response to treatment.

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TABLE 1

SUMMARY OF FINDINGS

SUBGROUP	SUBGROUP NUMBERS	TREATMENT ALLOCATION HORMONE ALONE	TREATMENT ALLOCATION HORMONE PLUS VIGABATRIN
Prenatal, not chromosomal	53 33 responders (62%)	24 13 responders (54%)	29 20 responders (69%)
Prenatal chromosomal	67 36 responders (54%)	33 18 responders (55%)	34 18 responders (53%)
Prenatal total	120 69 responders (58%)	57 31 responders (54%)	63 38 responders (60%)
Perinatal	55 31 responders (56%)	26 12 responders (46%)	29 19 responders (66%)
Postnatal	18 8 responders (44%)	11 6 responders (55%)	7 2 responders (29%)
Other	26 20 responders (77%)	14 9 responders (64%)	12 11 responders (92%)
TOTALS	219 128 responders (58%)	108 58 responders (54%)	111 70 responders (63%)

This table shows a summary of numbers in each aetiological group with response to treatment by treatment group. The prenatal group is shown divided into not chromosomal, chromosomal (inc DNA) and in total.

TABLE 2 – PRENATAL part 1, excluding chromosomal and DNA

Subgroup	Specific disease	Numbers	Responders
Malformations if not chromosomal	Agenesis of the corpus callosum	2	0
	Cerebellar dysplasia	1	1
	Cortical dysplasia	8	7
	Dysmorphic	1	1
	Hemispheric malformation	1	1
	Hemispheric dysplasia	1	1
	heterotopia	1	1
	holoprosencephaly	1	0
	Lissencephaly	9	4
	Microcephaly	5	1
	Neuronal migration defect	1	
	pachygyria	1	
	Periventricular nodular heterotopia	3	2
	Polymicrogyria	1	1
	Septo-optic dysplasia	1	1
	Small cerebral hemisphere	1	
	Thin corpus callosum	3	2
ventriculomegaly	1	1	
Other malformations (specific diseases)	Neurofibromatosis	1	1
	Tuberous Sclerosis	5	3
	Crouzon's	1	0
	Kabuki syndrome	1	1
Other	arthrogryposis	1	1
	Infection CMV	1	1
	Stroke or infarct	1	1

This table shows the number of infants with each specific disease and with response to treatment. There were 120 infants in the prenatal group including chromosomal with 66 responders (56% response rate).

CMV = cytomegalovirus

TABLE 2 – PRENATAL part 2, CHROMOSOMAL (including DNA)

Subgroup	Specific disease	Numbers	Responders
Chromosomal	47XXX	2	1
	47XXY	1	1
	ARX mutation	1	1
	Col 4A1 mutation	1	0
	del 16p 13.11	2	2
	del 1p36, dup 14q32	1	1
	del 3p26.3	1	0
	del 7p	1	1
	del 7q 11.23	1	1
	del 9p24 dup 11p13	1	1
	Down's syndrome	37	20
	dup 15	1	1
	dup 16p 13.3	1	0
	dup 16p11.2, del 7q31.1	1	1
	Dup 2p(inc NRXN 1)	1	1
	dup 3q29	1	0
	idic 15 (47, XX, + idic(15)(q13))	1	1
	familial neuromuscular disorder	1	1
	mitochondrial disorder	3	1
	Partial trisomy 15	1	0
	Partial trisomy 16 AND partial monosomy 18	1	0
	Rea 11q 24	1	0
	Ring chromosome 14	1	0
	STXB1 gene mutation	1	0
	STXBPA mutation	1	1
	Tetrasomy 15q	1	1
	Trisomy 5p	1	1

This table shows the number of infants with each specific disease and with response to treatment.

Del = deletion, dup= duplication, idic=isodicentric, Rea=re-arrangement.

TABLE 3 PERINATAL

Subgroup	Specific disease	Numbers	Responders
	HIE	24	16
	Intracranial non-traumatic haemorrhage	2	2
	IVH	3	0
	Maternal factors - drug abuse	1	0
	meningitis	1	0
	microcephaly	1	0
	PPHN - bleed into choroid plexus and ventricular dilatation	1	0
	PVH/PVL	8	6
	Stroke or infarct	3	1
	Transient endocrine or metabolic disease - hypoglycaemia	11	6

This table shows the number of infants with each specific disease in the perinatal group and with response to treatment. There were 55 infants in the group with 31 responders (56%).

HIE = Hypoxic Ischaemic Encephalopathy, IVH = intraventricular haemorrhage, PPHN = persistent pulmonary hypertension of the newborn, PVL/PVH = Periventricular leucomalacia/periventricular haemorrhage.

TABLE 4 – POSTNATAL

Subgroup	Specific disease	Numbers	Responders	
Endocrine or metabolic	Acyl Co-A dehydrogenase deficiency	1	1	
	Amino aciduria (propionicacidaemia)	1	1	
	B12 deficiency	1	1	
	CSF neurotransmitter disease	1	0	
	Lactic acidosis (not further specified)	1	0	
	Low folinic acid	1	0	
	Menke's disease	1	0	
	Mitochondrial disease	3	1	
	Organic aciduria (methylmalonic)	1	1	
	Serene deficiency	1	0	
	External injury	Trauma or non-accidental	3	1
		Nervous system	Encephalitis	1
	Meningitis		2	2

This table shows the number of infants in the postnatal group with each specific disease and with response to treatment. There were 18 infants in the postnatal group with 8 responders (44%).

CSF = cerebrospinal fluid.

TABLE 5 – OTHER GROUP

Subgroup	Specific disease	Numbers	Response
	Bilateral vocal chord paralysis	1	1
	Brain neoplasm - benign (hypothalamic hamartoma)	1	0
	Endocrine or metabolic - hypothalamic hypothyroidism	1	0
	Leukodystrophy	1	1
	Macrocephaly	1	1
	Microcephaly	3	2
	Neurodegenerative disorder	1	1
	Sensoryneural deafness	1	0
	Stroke or infarct	13	12
	Subdural collection	1	1
	Unexplained calcification	1	0
	White matter volume loss	1	1

This table shows the number of infants in the other group with each specific disease and with response to treatment. There were 26 infants in the other group with 20 responders (77%).

TABLE 6

Multivariable logistic regression of early clinical response in the proven aetiology group comparing those with stroke to those without stroke.

	Responders Day 14-42	Adjusted Odds Ratio (95%CI)	p value
Stroke		5.1 (1.1 to 23.6)	0.037
Present	14 / 17		
Absent	114/202		
Treatment modality		1.6 (0.9 to 2.8)	0.01
Combination	70 / 111		
Hormonal	58 / 108		
Lead time		0.5 (0.3 to 0.9)	0.012
< 28 days	91 / 140		
> 28 days	36 / 76		

* 3 children did not have a lead-time to treatment recorded

TABLE 7

Multivariable logistic regression of early clinical response in the proven aetiology group comparing those with Down's syndrome to those without Down's syndrome.

	Responders Day 14-42	Adjusted Odds Ratio (95% CI)	p value
Down's		0.8 (0.4 to 1.7)	0.62
Present	20 / 37		
Absent	108 / 182		
Treatment modality		1.5 (0.9 to 2.6)	0.15
Combination	70 / 111		
Hormonal	58 / 108		
Lead-time		0.8 (0.7 to 0.98)	0.03
< 28 days	91 / 140		
> 28 days	36 / 76		

* 3 children did not have a lead-time to treatment recorded

TO BE PUBLISHED AS A WEB APPENDIX ONLY

The following tables (1A, 2A, 3A, 4A and 5A) show the number of infants for each specific disease with treatment allocation and response to allocated treatment. Response is given by treatment allocation using two definitions of response: 14-42 refers to the ICISS definition of response (no observed spasms on and between Days 14-42) and 13-14 to the UKISS definition of response (no observed spasms on Days 13 and 14). Abbreviations are listed with the relevant tables in the main published text.

TABLE 1A – PRENATAL part 1, excluding chromosomal and DNA

PRENATAL GROUP n=120, ICISS responders 66 (56%)														
UKISS responders 96 (80%)														
Subgroup	Specific disease	n	Prednisolone alone			Tetracosactide Depot alone			Prednisolone with vigabatrin			Tetracosactide depot with vigabatrin		
14-42 refers to the ICISS definition of response 13-14 refers to the UKISS definition of response		n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	
Malformations if not chromosomal	Agenesis of the corpus callosum	2	1	0	0				1	0	0			
	Cerebellar dysplasia	1							1	1	1			
	Cortical dysplasia	8	4	3	3	1	1	1	2	2	2	1	1	
	Dysmorphic	1							1	1	1			
	Hemispheric malformation	1										1	1	
	Hemispheric dysplasia	1	1	1	1									
	heterotopia	1	1	1	1									
	holoprosencephaly	1				1	0	0						
	Lissencephaly	9	3	1	1	1	1	1	4	1	4	1	1	
	Microcephaly	5	2	0	1				3	1	2			
	Neuronal migration defect	1							1	0	1			
	pachygyria	1							1	1	1			
	Periventricular nodular heterotopia	3	1	0	0				1	1	1	1	1	
	Polymicrogyria	1							1	1	1			
	Septo-optic dysplasia	1							1	1	1			
	Small cerebral hemisphere	1										1	1	
	Thin corpus callosum	3	2	2	2				1	0	1			
ventriculomegaly	1	1	1	0										
Other malformations (specific diseases)	Neurofibromatosis	1									1	1		
	Tuberous Sclerosis	5	3	1	1				1	1	1	1		
	Crouzon's	1	1	0	1									
	Kabuki syndrome	1							1	1	1			
Other	arthrogryposis	1									1	1		
	Infection CMV	1							1	1	1			
	Stroke or infarct	1	1	1	1									

TABLE 2A – PRENATAL part 2, CHROMOSOMAL including DNA

Subgroup	Specific disease	n	Prednisolone alone			Tetracosactide depot alone			Prednisolone with vigabatrin			Tetracosactide depot with vigabatrin		
			n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	n	14-42	13-14
14-42 refers to the ICISS definition of response 13-14 refers to the UKISS definition of response														
	Chromosomal													
	47XXX	2	1	0	0							1	1	1
	47XXY	1							1	1	1			
	ARX mutation	1										1	1	1
	col 4A1 mutation	1							1	0	1			
	del 16p 13.11	2				1	1	1	1	1	1			
	del 1p36, dup 14q32	1				1	1	1						
	del 3p26.3	1							1	0	1			
	del 7p	1				1	1	1						
	del 7q 11.23	1	1	0	1									
	del 9p24 dup 11p13	1										1	1	1
	Down's syndrome	37	13	7	8	7	4	5	15	7	13	2	2	2
	dup 15	1				1	1	1						
	dup 16p 13.3	1										1	0	1
	dup 16p11.2, del 7q31.1	1	1	1	1									
	dup 2p(inc NRXN 1)	1							1	1	1			
	dup 3q29	1										1	0	0
	Isodicentric 15 (47, XX, + idic(15)(q13))	1												
	familial neuromuscular disorder	1							1	1	1			
	mitochondrial disorder	3	2	1	2				1	0	1			
	Partial trisomy 15	1							1	0	1			
	Partial trisomy 16 AND partial monosomy 18	1	1	0	1									
	Rea 11q 24	1	1	0	1									
	Ring chromosome 14	1										1	0	1
	STXB1 gene mutation	1										1	0	0
	STXBPA mutation	1										1	1	1
	Tetrasomy 15q	1	1	1	1									
	Trisomy 5p	1										1	1	1

TABLE 3A PERINATAL

Subgroup	Specific disease	N	Prednisolone alone			Tetracosactide Depot alone			Prednisolone with vigabatrin			Tetracosactide depot with vigabatrin		
			n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	n	14-42	13-14
14-42 refers to the ICISS definition of response 13-14 refers to the UKISS definition of response														
	HIE	24	5	3	3	3	2	2	10	5	9	6	6	5
	Intracranial non-traumatic haemorrhage	2	1	1	1							1	1	1
	IVH	3	3	0	2									
	Maternal factors - drug abuse	1	1	0	1									
	meningitis	1	1	0	0									
	microcephaly	1				1	0	0						
	PPHN - bleed into choroid plexus and ventricular dilatation	1							1	0	0			
	PVH/PVL	8	2	2	2	1	1	1	3	2	3	2	1	1
	Stroke or infarct	3	1	0	1	1	0	0	1	1	1			
	Transient endocrine or metabolic disease - hypoglycaemia	11	3	1	2	3	2	2	5	3	5			

TABLE 4A POSTNATAL GROUP

POSTNATAL GROUP n=18 ICISS responders 8 (44%) UKISS responders 11 (61%)														
Subgroup	Specific disease	n	Prednisolone alone			Tetracosactide depot alone			Prednisolone with vigabatrin			Tetracosactide depot with vigabatrin		
			n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	n	14-42	13-14
14-42 refers to the ICISS definition of response 13-14 refers to the UKISS definition of response			n	14-42	13-14	n	14-42	13-14	n	14-42	13-14	n	14-42	13-14
Endocrine or	Acyl Co-A dehydrogenase deficiency	1										1	1	1

