Comparison of treatment efficacy between oral steroid and ketogenic diet for patients with infantile spasm

Byoungho Noh

Department of Medicine

The Graduate School, Yonsei University

Comparison of treatment efficacy between oral steroid and ketogenic diet for patients with infantile spasm

Byoungho Noh

Department of Medicine

The Graduate School, Yonsei University

Comparison of treatment efficacy between oral steroid and ketogenic diet for patients with infantile spasm

Directed by Professor Heung Dong Kim

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the
degree of Master of Medical Science

Byoungho Noh

December 2013

This certifies that the Master's Thesis
of Byoungho Noh is approved.

Thesis Supervisor : Heung Dong Kim

Thesis Committee Member#1 : Joon Soo Lee

Thesis Committee Member#2 : Young Ho Lee

The Graduate School
Yonsei University

December 2013

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor, professor Heung Dong Kim for the encouraging and inspiring me to write this topic. I also would like to thank professor Young Ho Lee and professor Joon Soo Lee, whose advice were essential for me to complete this paper.

Also I like to thank my wife for having an exciting and happy life with me. In addition, thank you, my small boy for not disturbing me and waiting until finishing this paper.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Comparison of treatment efficacy between oral steroid and ketogenic diet for patients with infantile spasm

Byoungho Noh

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Heung Dong Kim)

Purpose: Infantile spasm is an age-dependent unique epilepsy syndrome characterized by clinical spasm, hypsarrhythmia at a particular age usually around 5 months. There are only few pharmacological and non-pharmacological treatments. Comparing the efficacy of oral steroid and that of ketogenic diet (KGD) may be beneficial to suggest which treatment should be considered first, in the early stage after pharmacological failure.

Methods: We reviewed 132 patients with infantile spasm who tried oral steroid or ketogenic diet treatments. We excluded children: who did not have typical hypsarrhythmia; who tried >3 anti-epileptic drugs (AEDs) before hormone or KGD; and who tried those treatments after 24-month old. Treatment efficacy was measured as seizure outcome in 3-month and long term final outcome: seizure free; >90% reduction; >50%; <50%; and no change.

Results: There was no difference in demographics between groups who tried hormone or KGD. Seizure outcome in 3 months was not statistically different between two groups. Median follow-up period was 3.1 years. Overall 17 of 54 (31.5%) patients evolved into Lennox-Gastaut syndrome (LGS). Eventual numbers of patients without seizure did not significantly differ between groups. Patients with seizure free in 3 months had been treated earlier with hormone/KGD after seizure-onset compared to those without (p=0.004). In addition, who responded better showed earlier response compared to who did not (p=0.015).

Conclusion: Ketogenic diet should be considered as early treatment option with a first line AED failure.

Key words: steroid, ketogenic diet, seizure, infantile spasm, efficacy

Comparison of treatment efficacy between oral steroid and ketogenic diet for patients with infantile spasm

Byoungho Noh

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Heung Dong Kim)

I. INTRODUCTION

Infantile spasms or West syndromes are well-known epilepsy syndrome since Dr. West described peculiar behaviors of his own son on 1841. These malignant epilepsy syndromes are typically characterized by its clinical spasms, hypsarrhythmia at a particular age usually around 5 months

Many researchers have been reported few drugs thought to be effective: adrenocorticotropic hormone (ACTH); oral steroid; vigabatrin[1-5]; and so on. Besides of these pharmacological treatments, there is also an effective non-pharmacological treatment for this syndrome, the ketogenic diet[6] (KGD). Researchers have pointed that patients with infantile spasm can be successfully treated by diet therapy, including modified types of ketogenic diet[7-9].

There were some reports comparing ketogenic diet and ACTH[10]. However, oral steroid can be good substitution for ACTH. Comparing the efficacy of ketogenic diet and that of oral steroid can give us useful insight of which treatment should be considered earlier if anti-epileptic drug (AED) fails.

II. SUBJECTS AND METHODS

Patients

We reviewed medical records retrospectively from children who visited Severance Hospital from January 2007 to October 2013. Reports of routine EEG, long-term video-EEG, CT scan, MRI, magnetic resonance spectroscopy (MRS) were reviewed. Each EEG was analyzed by more than two epileptologists. All reports of CT scan, MRI, and MRS were generated by more than two neuroradiologists.

Searching technique

All relevant records were obtained through computer-program designed for database searching and a keyword list. After keyword searching, each data was manually reviewed and assigned based on inclusion and exclusion criteria.

Inclusion and exclusion criteria

From Jan 2007 to October 2013, there were 6170 medical records for infantile spasm patient with a keyword of ketogenic diet and 8711 with hormone treatment (Fig. 1). Total 2789 records for ketogenic diet and 4259 for oral prednisolone created after patient-age of 24 months were excluded. From the rests of records, 69 patients experienced ketogenic diet and 80 patients of oral prednisolone before 24 month-old were included. After manual review of 132 patients, we excluded patients: who were tried more than 3 AEDs before hormone or ketogenic diet (n=41); who were on the hormone not for seizure control (n=27); without hypsarrhythmia (n=9); and who underwent epilepsy surgery before ketogenic diet during this period (n=1). The remaining 54 patient divided into two groups: oral steroid (hormone group, n=23); and ketogenic diet (KGD group, n=31).

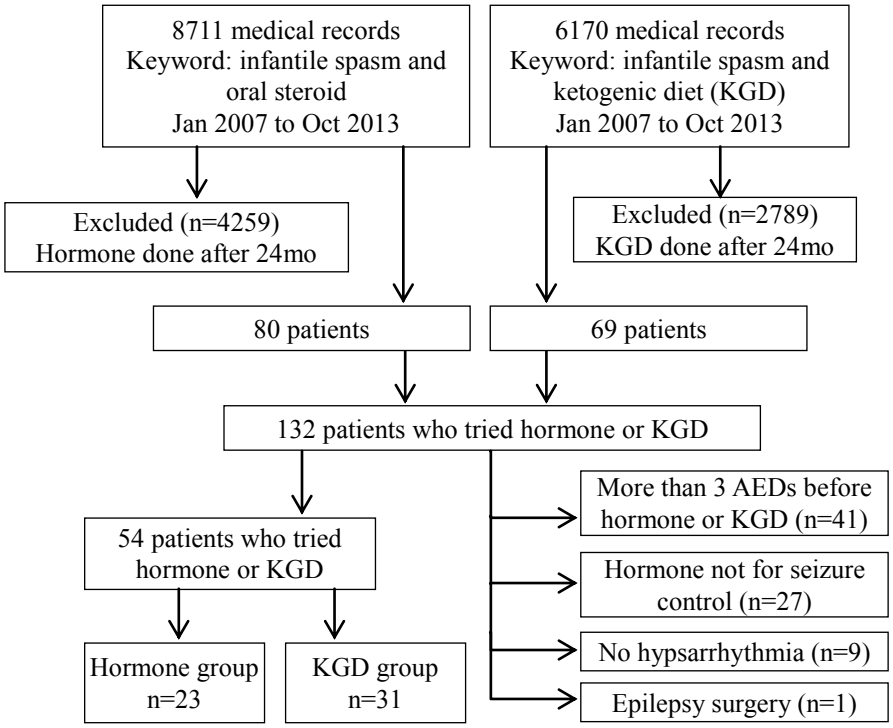

Figure 1. Diagram of inclusion/exclusion criteria
KGD, ketogenic diet; AED, antiepileptic drug

Data categorization

Treatment response was investigated at 3 month after treatments begin. Seizure outcome was located into: seizure free; >90% seizure reduction; 90~50% seizure reduction; <50% seizure reduction; and no change or even worse. EEG responses were categorized into: normalize; mildly abnormal EEG (rare or occasional interictal epileptiform discharges (IEDs) with mildly disorganized background); mild-to-moderately abnormal (more than occasional IEDs with an excess of background slowing); moderately abnormal (frequent IEDs with an excess of background slowing); and hypsarrhythmia. Spasm-free interval was estimated as weeks from the date of treatment begin to the last day of spasm within 12 weeks. Based on the 3-

Table 1. Demographics

	Total	Hormone	KGD	p-value *
Number	54	23	31	
Seizure onset age Median (month)	5.8	6.7	5.8	0.132
Negative MRI findings	22	7	15	0.188
Number of AEDs before Hormone/KGD (mean)	2.1	2.1	2.1	0.911
Sex(M/F)	29/25	12/11	17/14	0.847

*Mann-Whitney test
KGD, ketogenic diet; AED, antiepileptic drug

month response, the treatment latency from seizure onset to begin of hormone or KGD and efficacy from begin of treatment to spasm free were measured. Long term outcome was categorized into: seizure free; rare or less than monthly; monthly; weekly; daily; and death.

Statistical analysis

SPSS version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used for statistical analysis. Chi-square and Mann-Whitney test were used for categorical data. Ordinal data were analyzed by Kendall's tau (τ) coefficient for correlation analysis of seizure outcome and treatment latency (detail in tables).

III. RESULTS

Patient information

Overall 54 patients, 23 patients were treated by oral steroid and 31 by ketogenic diet (Table 1). Seizure-onset age was 5.8 in average without difference between two groups (p=0.132). Patients who have non-specific MRI findings were 22 and were not differently distributed (p=0.188). Average number of AEDs before oral steroid and ketogenic diet was 2.1 those were same in two groups. Sex ratio was similar in two groups.

Table 2. MRI findings and underlying etiology

	Total	Hormone	KGD
MRI	54	23	31
Normal	22 (40.7%)	7 (30.4%)	15 (48.4%)
PVL/HIE	14 (25.9%)	7 (30.4%)	7 (22.6%)
MCD/TSC	8 (14.8%)	3 (13.0%)	5 (16.1%)
Diffuse atrophy/dysmyelination	5 (9.3%)	2 (8.7%)	3 (9.7%)
Others[a]	5 (9.3%)	4 (17.4%)	1 (3.2%)
Etiology			
Undetermined	20 (37.3%)	7 (30.4%)	13 (41.9%)
Perinatal hypoxia	15 (27.8%)	8 (34.8%)	7 (22.6%)
MCD/TSC	8 (14.8%)	3 (13.0%)	5 (16.1%)
Metabolic	5 (9.3%)	1 (4.3%)	4 (12.9%)

PVL, periventricular leukomalacia; HIE, hypoxic ischemic encephalopathy; TSC, tuberous sclerosis complex; MCD, malformation of cortical development
[a]Cases include stroke and nonspecific gliosis.

Underlying etiology and MRI findings

Overall 40.7% of patient had reportedly normal MRI when diagnosed (Table 2). Almost one fourth of patients showed periventricular leukomalacia (PVL)/hypoxic ischemic encephalopathy (HIE). This proportion was similar in both groups (30.4% in hormone group and 22.6% in diet group). The second most common findings are similarly cortical malformation in hormone group (3, 13.0%) and diet group (5, 16.1%). While on the 37.3% of patient it was not able to find cause of epilepsy, determined causes of epilepsy were most commonly perinatal asphyxia/prematurity in more than a fourth of infants, followed by cortical malformation.

Table 3. Seizure response in 3 month follow up

	Total	Hormone	KGD	p-value *
Number	54	23	31	
Seizure free	34 (63.0%)	16 (69.9%)	18 (58.1%)	0.784
90% reduction	4 (7.4%)	1 (4.3%)	3 (9.7%)	
50% reduction	4 (7.4%)	1 (4.3%)	3 (9.7%)	
Less than 50%	4 (7.4%)	1 (4.3%)	3 (9.7%)	
No change	6 (11.1%)	4 (17.4%)	2 (6.5%)	

*Mann-Whitney test

Table 4. EEG response in 3 month follow up

	Total	Hormone	KGD	p-value *
Number	54	23	31	
Normalized	2 (3.7%)	0	2 (6.5%)	0.224
Mildly abnormal	8 (14.8%)	4 (17.4%)	4 (12.9%)	
Mild-to-moderately abnormal	13 (24.1%)	8 (34.8%)	5 (16.1%)	
Moderately abnormal	9 (16.7%)	2 (8.7%)	7 (22.6%)	
Hypsarrhythmic	22 (40.7%)	9 (39.1%)	13 (41.9%)	

*Mann-Whitney test

Treatment response

Almost two thirds of patients became seizure free within 3 months (Table 3). Totally 70% of patients favorably responded to those treatment; they were seizure free (34/54) or more than 90% seizures reduced (4/54). However, the numbers of who responded to the treatment in each group were not statistically different (p=0.784). The number of who partially responded was 8 (14.8%) in general.

Even though two EEGs were reportedly normalized in KGD group (Table 4), there was also no difference between groups (p=0.224). Overall half of

patients did not showed EEG improvement in short-term follow up.

In these patients, ten patients were tried both treatment one after another. Among who tried diet first, three out of four patients became seizure free after switching and one showed EEG response (mildly abnormal EEG). In other hands, six patient tried hormone first then switched. Four out of six patients became seizure free and three of them showed EEG response (mildly and mild-to-moderately abnormal EEG)

Latency of treatment and response

Spasm-free patients during first 3 months were 15/23 in hormone group and 21/31 in KGD group without significant difference (p=0.939). Among those patients, interval of spasm-free in 3 months, 3.1 weeks in hormone group and 3.2 weeks in KGD group which was not differ from each other (p=0.657).

Age of seizure onset was similar in groups: 5.9 months in seizure-free group; and 5.2 months in non-free group (Table 5). However interval from seizure-onset to treatments of hormone or KGD was 2.1 months in seizure free group and 5.0 months in non-free group, which was significantly different each other (p=0.004). In addition, interval from treatment initiation to treatment response date was significantly shorter (1.2 months) in children who became seizure free, compared to that of >90% group (5.3 months) and >50% group (8.9 months).

Table 5. Latency and seizure outcome

	Seizure free	Non seizure free				p-value
		>90%	>50%	<50%	No change	
Seizure onset age (median, month old)	5.9			5.2		0.991*
Seizure onset-to-treatment (median, month)	2.1			5.0		0.004*
Treatment-to-seizure free (median, month)	1.2	5.3	8.9	-	-	p=0.015† (tau-b =0.916)

*Mann-Whitney test, †Kendall's tau (τ) coefficient

Long term outcome

Median follow up age was 3.1 and ranged from 0.6 to 7.9 year-old which was similar between groups (p=0.263). The number of AEDs which were prescribed at the final visit was 1.0 in both of two groups (p=0.237). Who had eventually evolved into Lennox-Gastaut syndrome (LGS) were: 17/54 patients overall; 6/23 patients in hormone group; and 11/31 in KGD group which were not statistically different in those groups (p=0.560). Overall 31 patients were remaining seizure free and six patients had rare seizures only with illness (Table 6). There were twelve patients who reported daily seizures at the last visit. One patient who had hormone treatment and one ketogenic diet expired of aspiration pneumonia.

Table 6. Long term outcome

	Total	Group 1	Group 2	p-value *
Seizure free	31 (57.4%)	16 (69.6%)	15 (48.4%)	0.123
Rare than monthly[a]	6 (11.1%)	2 (8.7%)	4 (13.0%)	
Monthly	1 (1.9%)	1 (4.3%)	0	
Weekly	2 (3.7%)	1 (4.3%)	1 (3.2%)	
Daily	12 (22.2%)	2 (8.7%)	10 (32.3%)	
Death	2 (3.7%)	1 (4.3%)	1 (3.2%)	

*Mann-Witney test

[a]Cases include who only experience rare seizure with febrile illness

IV. DISCUSSION

The main finding of this study was that patients who treated earlier with hormone treatment or ketogenic diet showed better outcome after AED fail. Regardless which treatment was used, if the patient started hormone or diet earlier, those were more likely achieve seizure freedom. In addition, early responders were more likely to achieve better seizure control.

When an AED is tried first, there is a time needed to conclude efficacy. Failing of more AEDs are more delayed chance to try hormone or diet therapy. These findings are totally consistent with current knowledge that more failing initial AEDs suggest less possibility to be seizure free[11,12].

Currently ACTH is accepted as one of the first line treatment for infantile spasm in the U.S.[5], while oral steroid is the one of that in the U.K.[13]. Because the cost of ACTH treatment may be higher than $70,000 in the U.S.[14], this is clearly a barrier for ACTH to become more widely usable[15].

Furthermore, ACTH is not easily applicable in Korean clinical setting. Instead, other forms of steroid agents including oral prednisolone have been widely used as a substitution of ACTH formula. Because of this limitation, oral steroid and ketogenic diet are commonly considered as an early treatment option[8].

Patients who were treated differently did not respond differently during short follow-up period. The ratios of seizure response (free, >90%, etc.) was similar in two groups. More than 60% of patients were clinically seizure free. However, most common finding of EEG response to the treatment was unfortunately persistent hypsarrhythmia in 22 (40.7%) patients. Six (11.1%) patients who had persistent hypsarrhythmia eventually had seizure recurred shortest in two month after treatment stop.

Patients who respond well to the AEDs would not be treated by hormone or ketogenic diet. Therefore, individuals in present study may be biased patient who would have be more difficult to be treated by the first or second line AEDs. In literature, 20~65% of patient with infantile spasm evolve to LGS[16,17], which is variable according to underlying cause. Hormone treatment and/or ketogenic diet are known to possibly modify disease progress from infantile spasm evolution to LGS[18]. There were almost 30% of patients evolved into LGS and almost 60% of patients stayed seizure free in the present study. Even with these difficulties, these findings imply overall good outcome[7,15] in both groups of oral steroid and ketogenic diet.

Overall ten patients tried both treatments. Six patients tried oral steroid first, and four patients tried diet first. Among them, three patients were failed to treatments, one to hormone, and one to diet. Four out of six (66.7%) patients became seizure free after switching to KGD, and three out of four (75%) after to hormone.

Besides, there were two patients of prematurity and cortical malformation, who were already clinically seizure free after AED with persistent hypsarrhythmia. They were on diet therapy, because the patients' cognition did not improve. It is well known benefits that ketogenic diet can give a benefit in behavior and cognition[6,19]. After ketogenic diet, two patients showed mild-to-moderately abnormal EEGs with clinical improvement of cognition per care-giver's reports.

Overall 22 patients in hormone group and 16 in KGD were tolerable to those treatments. In hormone group, four patients underwent in-patient treatment: One for pneumonia; one for sepsis and stopped steroid; and two for vomiting/diarrhea. There was one patient diagnosed as Cushing syndrome who became seizure free. In KGD group, 21 patients were given in-patient treatment: four for respiratory infection and two stopped diet therapy; eleven for vomiting/diarrhea and two of them stopped KGD; four for decreased oral intake; one for persistent acidosis and stopped KGD; and one for transient blood tinged stool.

In summary, seizure freedom seems to be more easily achievable when those treatments were tried earlier after AED failure. In addition, early responders could have better seizure outcome. Treatment efficacy between hormone and ketogenic diet for infantile spasm did not show statistically significant difference. By these results, application of ketogenic diet for patients with infantile spasm could be recommended as early treatment option in addition to oral steroid in the current guideline[13].

V. CONCLUSION

Ketogenic diet should be considered as early treatment option with a first line AED failure.

REFERENCES

1. Chiron C, Dumas C, Jambaqué I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis1 This article has also been investigated by C. Allaire, P. Aubourg, M. Besson-Leaud, C. Cieuta, P. Damon, P. Danel, M. Derambure, I. Desguerre, M. Fohlen, J. Motte, P. Parisot, C. Pascal and A. de Saint-Martin.1. *Epilepsy Res.* 1997;26(2):389-395.
2. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice Parameter: Medical Treatment of Infantile Spasms: Report of the American Academy of Neurology and the Child Neurology Society. *Neurology.* May 25, 2004 2004;62(10):1668-1681.
3. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *The Lancet.* // 2004;364(9447):1773-1778.
4. Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *The Lancet Neurology.* 11// 2005;4(11):712-717.
5. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: Medical treatment of infantile spasms: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* June 12, 2012 2012;78(24):1974-1980.
6. Nordli DR, Kuroda MM, Carroll J, et al. Experience With the Ketogenic Diet in Infants. *Pediatrics.* July 1, 2001 2001;108(1):129-133.
7. Kossoff EH, Pyzik PL, McGrogan JR, Vining EPG, Freeman JM. Efficacy of the Ketogenic Diet for Infantile Spasms. *Pediatrics.* May 1, 2002 2002;109(5):780-783.
8. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. *Brain and Development.* 2006;28(9):566-571.
9. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience

in 104 consecutive infants. *Epilepsia.* Aug 2010;51(8):1403-1407.
10. Kossoff EH, Hedderick EF, Turner Z, Freeman JM. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. *Epilepsia.* 2008;49(9):1504-1509.
11. Krämer G. The limitations of antiepileptic drug monotherapy. *Epilepsia.* 1997;38(s5):S9-S13.
12. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? *Seizure : the journal of the British Epilepsy Association.* 2000;9(7):464-468.
13. Appleton RE, Freeman A, Cross JH. Diagnosis and management of the epilepsies in children: a summary of the partial update of the 2012 NICE epilepsy guideline. *Archives of Disease in Childhood.* December 1, 2012 2012;97(12):1073-1076.
14. Mytinger JR, Quigg M, Taft WC, Buck ML, Rust RS. Outcomes in Treatment of Infantile Spasms With Pulse Methylprednisolone. *J Child Neurol.* August 1, 2010 2010;25(8):948-953.
15. Kossoff EH, Hartman AL, Rubenstein JE, Vining EPG. High-dose oral prednisolone for infantile spasms: An effective and less expensive alternative to ACTH. *Epilepsy Behav.* 4// 2009;14(4):674-676.
16. Rantala H, Putkonen T. Occurrence, Outcome, and Prognostic Factors of Infantile Spasms and Lennox-Gastaut Syndrome. *Epilepsia.* 1999;40(3):286-289.
17. Camfield P, Camfield C. Long-term Prognosis for Symptomatic (Secondarily) Generalized Epilepsies: A Population-based Study. *Epilepsia.* 2007;48(6):1128-1132.
18. You SJ, Kim HD, Kang H-C. Factors influencing the evolution of West syndrome to Lennox-Gastaut syndrome. *Pediatric neurology.* 2009;41(2):111-113.
19. Kinsman SL, Vining EPG, Quaskey SA, Mellits D, Freeman JM. Efficacy of the Ketogenic Diet for Intractable Seizure Disorders: Review of 58 Cases. *Epilepsia.* 1992;33(6):1132-1136.

영아연축 환아에서 경구 스테로이드와 케톤생성 식이요법의 치료 효과 비교

<지도교수 김 흥 동>

연세대학교 대학원 의학과

노 병 호

연구목적: 영아연축은 특정 나이에 발생하는 뇌전증 증후군으로 연축 양상의 발작과 고부정뇌파를 특징으로 하며, 생후 5개월에 호발한다. 소수의 약물 혹은 비-약물 치료방법만이 존재한다. 경구 스테로이드의 치료효과와 케톤생성식이의 치료효과를 비교하는 것이 약물치료에 치료 실패 시에 다음단계의 치료법을 결정하는 데 유용할 것이다.
연구방법: 2007년 1월에서 2013년 10월까지 세브란스 병원에 내원하여 영아연축을 진단받고 경구 스테로이드 혹은 케톤생성 식이요법으로 치료받은 132명의 환아를 대상으로 하였다. 고부정뇌파가 관찰되지 않은 환아, 치료초기에 3가지 이상의 약물을 사용한 환아, 24개월 이후에 상기 치료법을 시행한 환아는 제외하였다. 치료효과의 판정은: 발작 없음; 90%이상 감소; 50%이상 감소; 50%이하 감소; 그리고 변화 없음으로 평가하였다.
결과: 경구호르몬을 사용한 군과 식이요법을 시행한 군과의 특성에 차이는 없었다. 3개월의 발작은 두 군간에 유의한 차이를 보이지 않았다. 총 추적관찰 기간은 3.1년이었다. 총 54명중 17명이 레녹스-가스토 증후군으로 이행하였다. 최종적으로 발작이 없는 환자의 숫자는 두 군간에 유의하게 차이를 보이지 않았다. 치료 시작 후 3개월에 발작이 소실된 환아는 그렇지 않는 환자들에 비해서 발작시작-치료시작 기간이 유의하게 짧았다 (p=0.004). 더하여, 발작의 조절이 더 양호한 환자는 그렇지 않은 환자에 비해서 치료효과가 더 일찍 나타났다 (p=0.015)
결론: 일차약제의 실패 이후 식이요법을 빨리 시도하는 것이 고려되어야 할 것이다.

핵심 되는 말: 스테로이드, 케톤생성식이, 발작, 영아연축, 치료효과