미토콘드리아 호흡연쇄 복합체 결함이 동반된 난치성 소아 뇌전증에서의 Zonisamide 부가 요법

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Zonisamide Adjunctive Therapy in Intractable Childhood Epilepsy with Mitochondrial Respiratory Chain Complex Defects

Purpose: Zonisamide (ZNS) is a broad-spectrum antiepileptic drug (AED). Free radical scavenging is also a possible action mechanism of ZNS. As oxidative stress plays an important role in the pathogenesis of mitochondrial cytopathy, we studied the efficacy and safety of ZNS as possible long-term adjunctive therapy in intractable childhood epilepsy with mitochondrial respiratory chain complex (MRC) defects.

Methods: MRC defects were confirmed by biochemical assays with muscle biopsies. We evaluated seizure frequencies and adverse effects in 38 childhood epilepsy patients with MRC defects who were maintained on ZNS for at least 12 months. Patients with more than 50% seizure reduction after 12 months were defined as responders.

Results: As for clinical diagnosis of mitochondrial cytopathy, 13 cases (34.2%) were diagnosed as Leigh syndrome and the remaining 25 (65.8%) had uncategorized mitochondrial cytopathy with nonspecific encephalopathy. The response rates for each seizure type after 12 months of ZNS therapy ranged from 23.1 to 55.6%; partial seizures (55.6%; 10/18), absence seizures (50.0%; 2/4), tonic-clonic seizures (40.0%; 2/5), atonic seizures (36.4%; 4/11), spasms (33.3%; 2/6), tonic seizures (31.8%; 7/22) and myoclonic seizures (23.1%; 3/13). The response rate for epileptic syndromes such as West syndrome and Lennox-Gastaut syndrome after ZNS treatment are 33.3% and 55.6% respectively. Somnolence, irritability, anorexia and weight loss were noticed as adverse effects, but all were transient.

Conclusion: ZNS could be an effective and safe candidate for adjunctive therapy in intractable childhood epilepsy with MRC defects. It could be considered preferentially for its free radical scavenging effect.

Key Words: Zonisamide, Epilepsy, Mitochondria, Respiratory chain, Free radical

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Introduction

Nonspecific encephalopathy associated with mitochondrial cytopathy tends to lead to progressive global dysfunction and increases cortical excitability, resulting in epilepsy¹⁾. Interestingly, in many cases of children with progressive epilepsy, the etiology is never fully identified. There have been suggestions of primary and secondary mitochondrial dysfunctions contributing to the development of epile-

psy^{2,3}). Many types of mitochondrial diseases have been associated with various epileptic conditions^{4,5}.

Oxidative stress is defined as an impairment of cellular function by free oxygen radicals. Under normal circumstances, the mitochondrial respiratory chain complex (MRC) would generate few free oxygen radicals by oxidative phosphorylation but in cases with MRC defects, the level of free oxygen radicals tends to increase markedly. Since free radicals happen to be particularly prevalent in brain tissue, its mitochondria are exposed to oxidative stress^{3,6}.

Zonisamide (ZNS), 1,2-benzisoxazole-3-methanesulfonamide, is a broad-spectrum antiepileptic drug (AED) for the treatment of multiple seizure types. In various neuropharmacological studies, ZNS was found to block voltage-sensitive Na and T-type calcium channels, modulate the dopaminergic system, and accelerate γ -aminobutyric acid release from hippocampus^{7,8}. It has also been suggested that the anticonvulsant effect of ZNS may involve protecting neurons from free radical damage by scavenging hydroxyl and nitric oxide radicals^{9,10}.

The purpose of this study was to evaluate the efficacy and safety of ZNS as long-term adjunctive therapy in intractable childhood epilepsy patients with MRC defects.

Materials and Methods

We studied 38 childhood intractable epilepsy patients with MRC defects treated with adjunctive ZNS at Gangnam Severance Hospital, with a follow up period from March 2012 to February 2016. Further data including seizure type and epilepsy syndrome, using the International League Against Epilepsy (ILAE) classification¹¹⁻¹³, antiepileptic medications and response to treatment were also obtained. Intractable epilepsy was defined as epilepsy in which seizures persist despite adequate trials of two tolerated, appropriately chosen and already used AEDs according to ILAE consensus proposal¹⁴. All patients experienced more than 4 seizures per month that were uncontrolled, even with a combination of 2 or more AEDs.

The MRC defects were confirmed by mitochondrial enzyme activity assay from muscle biopsy in all cases. Mitochondrial enzyme functions were evaluated using methods described by Rustin et al, analyzing the activities of reduced nicotinamide adenine dinucleotide (NADH)-coenzyme Q (CoQ) reductase (complex I), succinate-CoQ reductase (complex II), succinate-cytochrome c reductase (complex II-III), cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), oligomycin-sensitive ATPase (complex V), and citrate synthase assessed in

isolated mitochondria from muscle tissue using standard spectrophotometric assays^{15,16}. We defined an MRC defect as the reduction of residual enzyme activity below 20% of that in controls.

Baseline seizure frequency was determined by asking caregivers to count different seizure types separately during the month before the initiation of ZNS. Then, the frequency of each seizure type and adverse events were evaluated during each visit to the clinic by asking the caregivers during the follow-up period, relative to the baseline. The efficacy of treatment was determined by assessing the total monthly seizure frequency and individual seizure types at 12 months after ZNS initiation. Patients were classified into the following four categories, according to the percentage of seizure reduction: (1) seizure-free; (2) seizure reduction $\geq 50\%$; (3) seizure reduction $< 50\%$; and (4) no change or aggravation of seizures. Patients with more than 50% seizure reduction were defined as responders. Safety were assessed by evaluating adverse events reported by the patients and their caregivers during ZNS therapy. There were no exclusion criteria.

All patients were retrospectively reviewed for demographic data, seizure type, previous AED exposure, ZNS dose, duration of treatment, seizure frequency, and adverse effects. The study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine.

Results

1. Clinical features and ZNS treatment profile

Of the 38 patients with MRC defects, there were 21 boys and 17 girls, making the male-to-female ratio 1.24:1. The mean age of patients was 4.81 ± 2.64 years (range, 21-88 months). The mean age at seizure onset was 2.72 ± 2.26 years (range, 1-52 months) and the mean age at beginning medication was 3.24 ± 2.59 years (range 8-71 months).

The mean initial dosage of ZNS was 3.14 ± 1.76 mg/kg/day (range, 0.25-5.00 mg/kg/day). Doses were titrated up weekly. The mean dosage of maximum effectiveness was 10.24 ± 4.89 mg/kg/day (range, 3.0-15.0 mg/kg/day). The mean follow-up period after ZNS treatment initiation was 17.6 ± 7.40 months (range, 12-28 months). All patients had been receiving concomitant AEDs (mean, 3.42 ± 1.77 ; range, 2-5) at the time of starting ZNS treatment (Table 1).

2. Biochemical and clinical diagnosis of mitochondrial cytopathy

The most common type of MRC defect was complex I, observed in 27 cases (71.0%), followed by complex IV in 11 (29.0%). As for the clinical diagnosis of mitochondrial disorders, 13 cases

(34.2%) were diagnosed with Leigh syndrome. However, 25 cases (65.8%) could not be diagnosed as specific clinical mitochondrial syndrome (Table 2).

3. Neuroimaging study

In brain magnetic resonance imaging (MRI) findings, diffuse cortical atrophy was the most common observation and was seen in 29 cases (76.3%). Abnormal signal change of the basal ganglia was seen in 14 cases (36.8%), signal change of the thalamus in 11 (28.9%), brain stem signal changes in 8 (21.1%), cerebellar atrophy in 8 (21.1%), and diffuse white matter dystrophy in 6 (15.8%) (Table 3). A definite lactate peak was observed in 13 out of 38 cases (34.2%) when examined by proton MR spectroscopy.

4. Efficacy of ZNS

The various seizure types included 22 cases (57.9%) of tonic seizures, 18 (47.4%) partial seizures, 13 (34.2%) myoclonic seizures, 11 (28.9%) atonic seizures, 6 (15.8%) spasms, 5 (13.2%) tonic-clonic seizures and 4 (10.5%) absence seizures. Epilepsy syndrome classifications included 6 cases (15.8%) of West syndrome and 9 (23.7%) Lennox-Gastaut syndrome (LGS). Others were difficult to classify definite criteria of certain epileptic syndrome (Table 1). Interictal electroencephalography features were variable among patients but background abnormalities and epileptiform discharge were observed in all.

Table 1. Clinical Profiles of Patients (N=38)

Age (mean)	3.92±2.44 years
Male/Female (N, ratio)	21/17, 1.24:1
Seizure onset age	2.72±2.26 years
Developmental delay	38 cases (100%)
Initial mean ZNS dose	3.14±1.76 mg/kg/day (0.25-5.00 mg/kg/day)
Mean maximum effective dose	10.24±4.89 mg/kg/day (3.0-15.0 mg/kg/day)
Mean follow up after initiation of ZNS	17.6±7.40 months (range, 12-28 months)
Concomitant AEDs at the time of initiation of ZNS	Mean, 3.42±1.77 (range, 2-5)
Epilepsy syndromes	
West syndrome	6 (15.8%)
Lennox-Gastaut syndrome	9 (23.7%)
Seizure types	
Tonic	22 (57.9%)
Myoclonic	13 (34.2%)
Atonic	11 (28.9%)
Spasm	6 (15.8%)
Tonic-clonic	5 (13.2%)
Absence	4 (10.5%)
Partial	18 (11.1%)

ZNS, zonisamide; AED, antiepileptic drug.

The response rates for each seizure type after 12 months of ZNS therapy are presented in table 4. The response rates related to seizure type ranged from 23.1 to 55.6% at 12 months; partial seizures (55.6%; 10/18), absence seizures (50.0%; 2/4), tonic-clonic seizures (40.0%; 2/5), atonic seizures (36.4%; 4/11), spasms (33.3%; 2/6), tonic seizures (31.8%; 7/22) and myoclonic seizures (23.1%; 3/13). Responder rates were highest among children with partial seizures. The response rate for each epileptic syndromes such as West syndrome and Lennox-Gastaut syndrome after the introduction of ZNS are 33.3% and 55.6% respectively (Table 5).

5. Safety of ZNS

During our study, 5 patients suffered somnolence, and 4 had irritability. There were 2 cases of anorexia and one of weight loss (Table 6). However, the degree of adverse event was not severe

Table 2. Results of Biochemical Enzyme Assay and Clinical Diagnosis (N=38)

Enzyme deficiency	Clinical diagnosis		No. of patients (%)
	Leigh syndrome	Uncategorized	
MRC I	8 (21.0)	19 (50.0)	27 (71.0)
MRC IV	5 (13.2)	6 (15.8)	11 (29.0)
Total	13 (34.2)	25 (65.8)	38 (100.0)

MRC, mitochondrial respiratory chain complex.

Table 3. Findings of Brain Magnetic Resonance Imaging (N=38)

MRI findings	No. of patients (%)
Diffuse cortical atrophy	29 (76.3)
Basal ganglia change	14 (36.8)
Thalamus change	11 (28.9)
Brain stem change	8 (21.1)
Cerebellar atrophy	8 (21.1)
White matter change	6 (15.8)

MRI, magnetic resonance imaging.

Table 4. Responses by Seizure Types to Zonisamide Adjunctive Therapy

Seizure types	N	Seizure free (%)	≥ 50% seizure reduction (%)
Tonic	22	1/22 (4.5)	7/22 (31.8)
Myoclonic	13	1/13 (7.7)	3/13 (23.1)
Atonic	11	1/11 (9.1)	4/11 (36.4)
Spasm	6	1/6 (16.7)	2/6 (33.3)
Tonic-clonic	5	0/5 (0.0)	2/5 (40.0)
Absence	4	0/4 (0.0)	2/4 (50.0)
Partial	18	2 (11.1)	10/18 (55.6)

Table 5. Responses of West Syndrome and Lennox-Gastaut Syndrome to Zonisamide Adjunctive Therapy

Epilepsy syndromes	N	Seizure free (%)	≥ 50% seizure reduction (%)
West syndrome	6	1/6 (16.7)	2/6 (33.3)
Lennox-Gastaut syndrome	9	0/9 (0.0)	5/9 (55.6)

enough to stop the medication. All adverse events were transient and successfully managed by careful follow up.

Discussion

There have been few reports about the treatment efficacy of AEDs in epilepsy patients with MRC defects, thus making us hard to compare our study results^{5,17}. On the other hand, studies on refractory epilepsy without MRC defects have been reported in quite numbers. Previous reports showed that 22–44% of pediatric patients who were refractory to existing AEDs experienced $\geq 50\%$ reduction in partial seizure frequency, and 9–18% in generalized seizure on ZNS adjunctive therapy¹⁸. Compared to those reports, 10 out of 18 patients (55.6%) experienced $\geq 50\%$ reduction in partial seizure frequency and 23.1–50% of patients with generalized seizures of various seizure type showed $\geq 50\%$ reduction. This implies that adjunctive treatment with ZNS can be effective in intractable childhood epilepsy patients with MRC defects.

Studies on responder rate of ZNS in infantile spasm have also been reported. It was reported that 22% of patients showed $\geq 50\%$ seizure reduction, while others reported that 36% of patients with infantile spasm experienced complete cessation of seizure and disappearance of hypsarrhythmia after treating ZNS^{19,20}. Reports concerning ZNS efficacy on LGS can also be spotted. Three independent studies were done in Japan, evaluating a total of 77 children with LGS. The response rate to ZNS was 26%, 50% and 54%, respectively^{21–23}, with 35% (27/77) of patients attaining at least a 50% reduction in seizure frequency²⁴. In Korea, 62 patients with LGS receiving ZNS were evaluated and 32 patients (51.6%) among them were reported to have experienced $>50\%$ reduction in seizure frequency, regardless of seizure type and etiology²⁵. In our study, the rate of seizure reduction over 50% were 33.3% (2/6) and 55.6% (5/9) after ZNS therapy in catastrophic epileptic syndrome such as West syndrome and LGS respectively. The result of our study, though analyzed in a small number of cases, is not bad at all even when compared to other study results, considering the fact that patients were suffering MRC defects along the way. We believe that this supports the role of ZNS as possible candidate of initial or add on treatment modality.

The antiepileptic efficacy and tolerability of ZNS in epilepsy patients with MRC defects are thought to be related to its free radical scavenging activities. The hydroxyl radical is capable of damaging protein, carbohydrates, and deoxyribonucleic acid (DNA), and is known to be the most harmful radical for neuro-membranes. Free radical scavenging activities of ZNS for hydroxyl and nitric oxide radicals were clearly demonstrated *in vitro*^{9,10}. Mitochondria are known to be the most important source of production of reactive oxygen species. Some suggest that chronic mitochondrial oxidative stress and resultant dysfunction are sufficient to cause an increase in seizure susceptibility while others suggest that mitochondrial oxidative stress can be a consequence of epileptic seizures, possibly contributing to persistent mitochondrial dysfunction observed in the epileptic brain^{26,27}. In the former case, ZNS can be speculated as a tool for antiepileptogenic treatment rather than antiepileptic treatment. In the latter case, it serves as a neuroprotective agent to prevent progressive neuronal cell death.

Moreover, major adverse events of the drug were not observed in our study. The most commonly reported adverse events of ZNS include somnolence, anorexia, ataxia, irritability, insomnia, headache, weight loss, oligohydrosis, and renal calculi^{24,28}. Though somnolence and irritability were experienced by a few subjects, they were not severe enough to discontinue ZNS treatment. Therefore, ZNS could be considered safe to use in intractable childhood epilepsy patients with MRC defects.

Since MRC defect itself is a rare disease entity and identification or diagnosis of mitochondrial dysfunction is relatively difficult, the numbers of our study cases were small numbered and could not be conducted as randomized controlled study. So, in order to confirm ZNS as a possible treatment for intractable epilepsy patients with MRC defects, more systematic studies and analysis on antiepileptic drug efficacy would be needed. Also, the importance of finding the exact etiology of uncontrolled epilepsy should never be underestimated, since it is the first step to find the most appropriate antiepileptogenic treatment. Among those treatment modalities, ZNS treatment could be considered as a promising approach against free oxygen radicals in epilepsy patients with MRC defects.

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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. The authors declare that there is no conflict of interest regarding the publication of this paper.

Table 6. Adverse Events of Zonisamide (N=38)

Adverse events	No. of patients (%)
Somnolence	5 (13.2)
Irritability	4 (10.5)
Anorexia	2 (5.3)
Weight loss	1 (2.6)

요약

목적: Zonisamide (ZNS)는 넓은 치료 범위의 항경련제이며, 유리기의 해독효과는 ZNS의 중요한 작용기전이다. 미토콘드리아 세포병증의 발병 기전에서 산화적 스트레스가 중요한 역할을 하기 때문에, 우리는 미토콘드리아 호흡연쇄 복합체 결함을 동반한 난치성 소아 뇌전증 환자에서 장기적인 항경련제 부가요법으로서 ZNS의 치료 효과와 안전성에 대하여 후향적 연구와 분석을 시행하였다.

방법: 미토콘드리아 호흡연쇄 복합체 결함이 확인된 난치성 소아 뇌전증 환자 중에서 최소 12개월 동안 ZNS 복용을 지속하였던 38명의 환자들을 대상으로 경련 횟수와 약물 부작용을 평가하였다. ZNS 복용 12개월 후 50% 이상의 경련 감소를 보인 환자를 약물 반응군으로 정의하였다.

결과: 전체 환자군에서 Leigh 증후군은 13례(34.2%)이었고, 나머지 25례(65.8%)는 비특이적 뇌병증을 동반한 분류되지 않은 미토콘드리아 세포병증이었다. 생화학적 분석에서 미토콘드리아 호흡연쇄 1번 복합체 결함이 27례(71.0%)이었고, 4번 복합체 결함이 11례(29.0%)였다. ZNS 치료 후 각 경련의 종류는 23.1-55.6%에서 50% 이상 빈도가 감소하였다. 부분 경련은 55.6% (10/18), 결신 경련은 50.0% (2/4), 강직-간대 경련은 40.0% (2/5), 탈력 경련은 36.4% (4/11), 연속은 33.3% (2/6), 강직 경련은 31.8% (7/22), 근간대성 경련은 23.1% (3/13)에서 50% 이상 빈도가 감소하였다. West 증후군과 Lennox-Gastaut 증후군 환자군에서의 ZNS 치료의 약물 반응군은 각각 33.3%와 55.6%이었다. ZNS 부작용으로는 졸림, 보챔, 식욕부진, 체중감소가 확인되었으나 모두 일시적이었다.

결론: 미토콘드리아 호흡연쇄 복합체 결함을 동반한 난치성 소아 뇌전증에서 ZNS는 항경련제 부가 요법으로서 효과적이고 안전한 약물로 사용될 수 있을 것이다. 미토콘드리아 세포병증을 동반한 뇌전증에서의 발생 기전을 고려하면, 유리기 해독효과를 가진 ZNS의 투여가 먼저 고려될 수도 있다.

References

- Schmiedel J, Jackson S, Schäfer J, Reichmann H. Mitochondrial cytopathies. *J Neurol* 2003;250:267-77.
- Kunz WS. The role of mitochondria in epileptogenesis. *Curr Opin Neurol* 2002;15:179-84.
- Patel M. Mitochondria dysfunction and oxidative stress: cause and consequence of epileptic seizures. *Free Radic Biol Med* 2004;37:1951-62.
- Kang HC, Kwon JW, Lee YM, Kim HD, Lee HJ, Hahn SH. Non-specific mitochondrial disease with epilepsy in children: diagnostic approaches and epileptic phenotypes. *Childs Nerv Syst* 2007;23:1301-7.
- Lee YM, Kang HC, Lee JS, Kim SH, Kim EY, Lee SK, et al. Mitochondrial respiratory chain defects: underlying etiology in various epileptic conditions. *Epilepsia* 2008;49:685-90.
- Cadenas E, Boveris A, Ragan CI, Stoppani AO. Production of superoxide radicals and hydrogen peroxide by NADH-ubiquinone reductase and ubiquinol-cytochrome c reductase from beef heart mitochondria. *Arch Biochem Biophys* 1977;180:248-57.
- Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure* 2004;13 Suppl 1:S5-9.
- Sills G, Brodie M. Pharmacokinetics and drug interactions with zonisamide. *Epilepsia* 2007;48:435-41.
- Mori A, Noda Y, Packer L. The anticonvulsant zonisamide scavenges free radicals. *Epilepsy Res* 1998;30:153-8.
- Noda Y, Mori A, Packer L. Zonisamide inhibits nitric oxide synthase activity induced by N-methyl-D-aspartate and buthionine sulfoximine in the rat hippocampus. *Res Commun Mol Pathol Pharmacol* 1999;105:23-33.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489-501.
- 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.
- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-85.
- Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069-77.
- Rustin P, Chretien D, Bourgeron T, Gérard B, Rötig A, Saudubray JM, et al. Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 1994;228:35-51.
- Chretien D, Rustin P, Bourgeron T, Rötig A, Saudubray JM, Munnich A. Reference charts for respiratory chain activities in human tissues. *Clin Chim Acta* 1994;228:53-70.
- Lee HF, Chi CS, Tsai CR, Chen CH. Epileptic seizures in infants and children with mitochondrial diseases. *Pediatr Neurol* 2011;45:169-74.
- Glauser TA, Pellock JM. Zonisamide in pediatric epilepsy: review of the Japanese experience. *J Child Neurol* 2002;17:87-96.
- Yagi K, Seino M. Methodological requirements for clinical trials in refractory epilepsies - our experience with zonisamide. *Prog Neuropsychopharmacol Biol Psychiatry* 1992;16:79-85.
- Suzuki Y, Nagai T, Ono J, Imai K, Otani K, Tagawa T, et al. Zonisamide monotherapy in newly diagnosed infantile spasms. *Epilepsia* 1997;38:1035-8.
- Sakamoto K, Kurokawa S, Tomita S, Chen A, Kitamoto I, Ueda H, et al. Therapeutic effects of zonisamide (AD-810) on infantile epilepsy. *Med Consult New Remedies* 1986;23:2571-2581.
- Yamatogi Y, Ohtahara S. Current topics on treatment. *New*

- Trends in Pediatric Epileptology. Okayama University Medical School. 1991. pp. 136-48.
- 23) Iinuma K, Haginoya K. Clinical efficacy of zonisamide in childhood epilepsy after long-term treatment: a postmarketing, multi-institutional survey. *Seizure*. 2004;13 Suppl 1:S34-9.
- 24) Ohtahara S. Zonisamide in the management of epilepsy-Japanese experience. *Epilepsy Res* 2006;68 Suppl 2:S25-33.
- 25) You SJ, Kang HC, Kim HD, Lee HS, Ko TS. Clinical efficacy of zonisamide in Lennox-Gastaut syndrome: Korean multicentric experience. *Brain Dev* 2008;30:287-90.
- 26) Kunz WS, Kudin AP, Vielhaber S, Blümcke I, Züschratter W, Schramm J, et al. Mitochondrial complex I deficiency in the epileptic focus of patients with temporal lobe epilepsy. *Ann Neurol* 2000;48:766-73.
- 27) Liang LP, Ho YS, Patel M. Mitochondrial superoxide production in kainite-induced hippocampal damage. *Neuroscience* 2000;101:563-70.
- 28) Mattson RH. The role of the old and the new antiepileptic drugs in special populations: mental and multiple handicaps. *Epilepsia* 1996;37 Suppl 6:S45-53.