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Review

Congenital Anomalies in the Offspring of Epileptic Mothers*

Yoshibumi NAKANE[1] and Sunao KANEKO[2]

[1]Department of Neuropsychiatry, Nagasaki University School of Medicine, 1-12-4 Sakamoto, Nagasaki 852, Japan and [2]Department of Neuropsychiatry, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036, Japan

ABSTRACT The incidences of various complications during pregnancy are not significantly different between epileptic and nonepileptic mothers in the majority of papers so far reported. More than 70 to 80% of women with epilepsy will have no change in seizure frequency, while 5% will have fewer seizures than before and the remaining patients will have more seizures during pregnancy provided that their drug compliance is good. Intrauterine growth, in particular, of head circumference of fetus is delayed. However, this retardation disappears within few years after birth. The risk of congenital malformations of the offspring born to treated epileptic mothers is greater than in the general population. Among risk factors for teratogenesis that had been considered to date, only antiepileptic drug (AED)-related factors had proved to be significantly related to the occurrence of malformations. Among AEDs, methylphenobarbital, valproate, primidone, carbamazepine and phenytoin are teratogenic, particularly when they are used in combination. Follow up EEG of children born to epileptic mothers revealed that the incidence of abnormal EEG was 44%, and 28 to 38% showed epileptiform patterns. Only 7% of offspring had epileptic seizures. In the offspring without clinical seizures revealed that most of the epileptiform patterns disappear after the age 10. Recommendations concerning AED therapy during pregnancy are also discussed.

Key words: epilepsy, malformation, congenital anomaly, pregnancy, antiepileptic drug, facial cleft

INTRODUCTION

Epilepsy is a common disease seen at psychiatric, neurology, pediatric and neurosurgical clinics. It is defined as "a clinical brain disorder of various etiologies characterized by recurrent seizures due to excessive discharge of cerebral neurons, [and is] associated with a variety of clinical and laboratory manifestations" (Gastaut, 1973). Its prevalence rate is 3-8 in 1,000 population, which means it is not rare. About 40% of patients are women who have the potential of becoming pregnant. Etiology can vary according

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中根允文，長崎大学医学部精神科，〒852 長崎市坂本1丁目12-4

兼子　直，弘前大学医学部精神神経科，〒036 弘前市在府町5

to the age of onset and other factors. Sometimes the pathology itself can be congenital.

Because of relationship between epilepsy and pregnancy, the influence of epilepsy on children needs to be correctly identified based on the results of strictly controlled studies of female epileptics who are pregnant, or may become pregnant. In particular, the following four factors are important. First, there is the problem concerning the extent to which epilepsy is hereditary. Second, there is the question of complications and congenital anomalies in children born of epileptic mothers. Third, there is a concern with the effect of epileptic seizures which appear during the pregnancy, both on the pregnancy itself and on the infants. Finally, as drug therapy is the main treatment for epilepsy, there is a concern with the influence of anti-epileptic drugs (AED) on the fetus and on the course and consequence of the pregnancy.

While the relationship between maternal disease and congenital anomalies is the main theme of this paper, the problem of heredity and the interaction between epilepsy and pregnancy is outlined. Next we present the results of our own research, done with the cooperation of other co-workers in Japan, on the effect of epilepsy and AED on the growth of the fetus and on congenital malformations, and other complications.

HEREDITY OF EPILEPSY

The study of the role of heredity factors includes family and twin studies. However, much of the data to date is not always useful as the classification of epilepsy and epileptic seizures is still under the process of revision. Despite this limiting factor, latest reports from Japan on this subject are as follows: Yamatogi and colleagues (1991) examined 79 children (1 month to 14.5 years old, 48 of whom were over 3 years of age) born of 48 epileptic mothers, and recognized convulsive seizures (include febrile convulsion) in 20% of them and paroxysmal abnormality of EEG in 27.8%. Further, among the 48 infants over 3 years of age, as many as 48% presented an abnormal EEG. Saito and colleagues (1991), who made a similar study on 39 children between the ages of 4 and 16 years, reported that 22% of them had convulsive seizures and 38% showed an abnormal EEG.

INTERACTION BETWEEN EPILEPSY AND PREGNANCY

1) Effect of Epilepsy on the Course of Pregnancy

Concern has been expressed that pregnancy in epileptic patients is more likely to be accompanied by various complications than that of a non-epileptic population. However, after reviewing reports so far published, it is noted that few have found significant differences, and thus it is hard to make definite conclusions. A most regrettable problem with these reports is that most studies have lacked a proper control group.

While it has been pointed out that epileptic women, compared to non-epileptic women, have a greater chance of experiencing a natural abortion before they can have their own babies (Hiilesmaa et al., 1985), the difference is not significant according to Annergers et al. (1988). In relation to pregnancy toxemia, Ogawa and colleagues (1984) reported a definitely higher incidence in epileptic patients, while others have found little difference. No difference has been found in the length of the prenatal period. Finally, pre-eclampsia was more frequent in patients, compared with a control group, and the frequency of cesarean section and vacuum extraction was generally higher in the patient group.

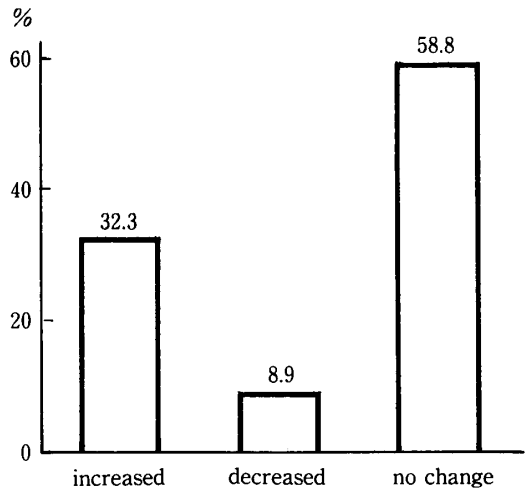

Fig. 1 Modification of seizure frequency during pregnancy

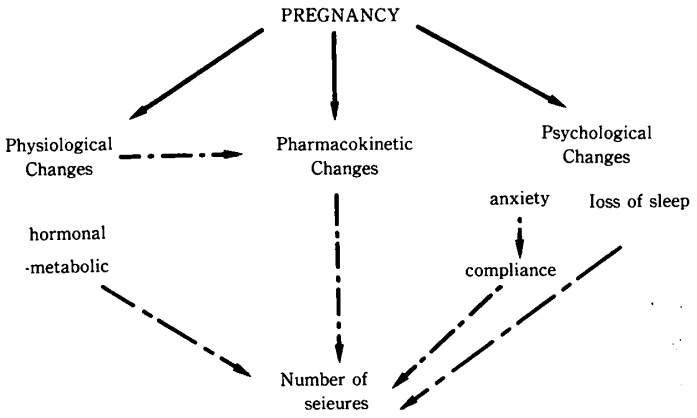

Fig. 2 Factors that may affect seizure frequency during pregnancy

2) Effect of Pregnancy on Epilepsy

When dealing with the effect of pregnancy on epilepsy, the increase or decrease in the frequency of epileptic seizures and the appearance of status epilepticus often become subjects of discussion. Figure 1 illustrates the results obtained from a multi-institutional cooperative study conducted in Japan (Nakane et al., 1980). It shows that seizure frequency did not changed in 59% of patients, increased in about 30% and decreased in nearly 10%. A similar tendency can be observed in the results obtained from other research. Levy and colleague (1985) have summarized the nature of changes in seizure frequency and this is illustrated in figure 2.

With the exception of some case reports, status epilepticus has not received much attention. Thus, further investigations are needed to determine the extent of its occurrence during pregnancy.

CONGENITAL ANOMALIES IN THE OFFSPRING OF EPILEPTIC MOTHERS

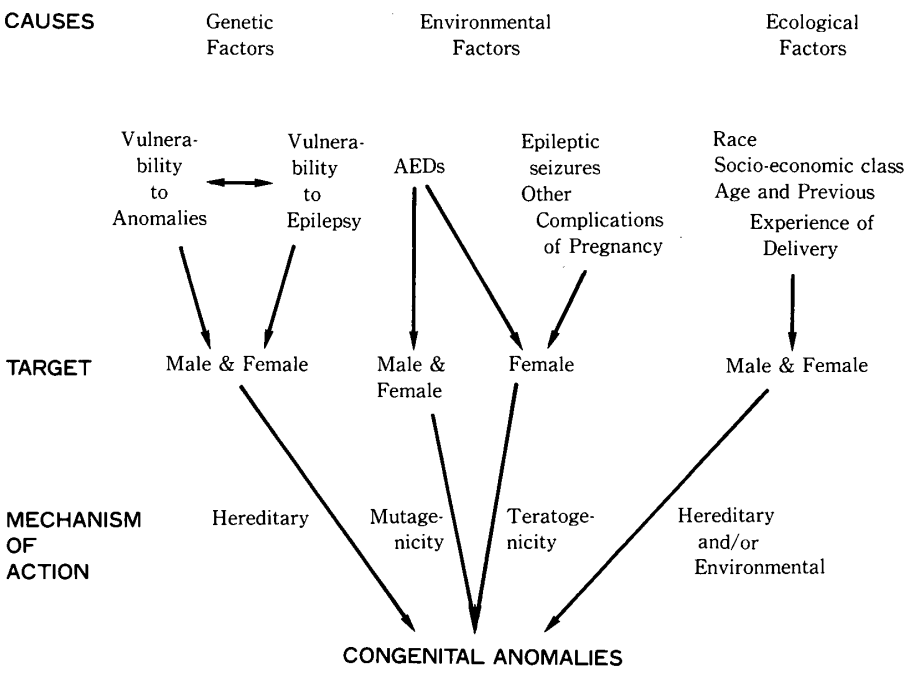

Fig. 3

EFFECT OF MATERNAL EPILEPSY OR INTAKE OF ANTIEPILEPTIC DRUGS ON INFANTS

1) On the Growth or Development of Children

In reference to birth weight as an indicator of fetal development, it has been reported that the appearance of the so-called 'premature baby', with a weight under 2500 g, is more frequent in epileptic patients (Bjerkedal and Bahna, 1973; Ogawa et al., 1984; Yerby et al., 1985). However other reports have found the opposite.

Research on the development of physical and psychological development suggests that height and head circumference in such children is significantly smaller, and that psychomotor development is also retarded. According to Nomura et al. (1984), who made a follow-up observation of development from birth to 36 months, most evidence of retardation disappears during the follow-up period, except that an improvement in speech development can be delayed if there is a poor family environment. Battino et al. (1991) examined a large number of cases and concluded that birth weight and head circumference are definitely smaller in patient than control groups. In particular, a small skull may be related to the number of AEDs used together.

2) On Congenital Malformations in Children

When we think about congenital malformation, it is necessary to take into account hereditary factors such as the presence of congenital malformation in parents and relatives; environmental factors concerning teratogenicity or mutagenicity, such as the effect of parental diseases on the pregnancy and that of

Table 1. Epilepsy among parents of children with facial cleft

authors	children with facial cleft	mothers with epilepsy	fathers with epilepsy	total
Dronamraju (1970)	295	(1st & 2nd degr. relatives)		52
Pashayan et al. (1971)	100	4 (4.00)		
South (1972)	16	2 (12.50)		
Erickson et al. (1974)	306	3 (0.98)		
Saxen (1975)	599	2 (0.33)		
Friis (1979)	391	11 (2.81)	7 (1.79)	18
Gadoth et al. (1987)	252	4 (1.59)		
Takahashi et al. (1989)	365	5 (1.40)		
total	2029	31 (1.52)		

Table 2. Incidence of malformations in children of mothers and in children of fathers with epilepsy*

	mothers with epilepsy			fathers with epilepsy		
	children	malformations		children	malformations	
authors	N	N	%	N	N	%
Meyer (1973)	313	51	16.3	270	30	11.1
Dansky (1974)	84	14	16.7	100	1	1.0
Shapiro (1974)	305	32	10.5	396	33	8.3
Annergers (1978)	259	21	8.1	128	5	3.9
Matsushima (1978)	103	4	3.9	82	4	4.9
Dietrich (1980)	37	0	0	22	0	0
Janz (1980)	397	61	15.4	371	41	11.1
total	1498	183	12.2	1369	114	8.3

*: Nakane Y. (1984)

the drugs to which the mother was exposed during the prenatal period; and finally ecological factors, such as race, social-economic class, mother's experience of and age at delivery (see figure 3). Thus, the role of genetic factors needs to be identified in order to determine the relationship between epilepsy and congenital malformation. For example, offspring of mothers being treated with AEDs are said to be more likely to have a facial cleft such as a cleft lip and/or palate. But in order to clarify whether these clefts are due to heredity factors or to the action of antiepileptic drugs, it is necessary to examine both the incidence rate of epilepsy in the patients with these anomalies and their relatives, and the frequency of facial cleft in epileptic patients themselves.

Dronamraju (1970) seems to have been one of the first to conduct research on this issue. He examined immediate and extended family members of infants with a facial cleft, and recognized epilepsy in 17.6%

Table 3. Malformation rates in the offfspring of epileptic and control mothers*

authors	control mothers malformation rate(%)	control mothers no. of pregnancies	epileptic mothers malformation rate(%)	epileptic mothers no. of pregnancies
Sabin & Oxorn (1956)			5.4	56
Janz & Fuchs (1964)			2.3	225
German et al. (1970)			5.3	243
Elshove & van Eck (1971)	1.9	12051	15.0	65
Speidel & Meadow (1972)	1.6	483	5.2	427
South (1972)	2.4	7892	6.4	31
Spellacy (1972)		50	5.8	51
Bjerkedal & Bahna (1973)	2.2	12530	4.5	311
Fedrick (1973)	5.6	649	13.8	217
Koppe et al. (1973)	2.9	12455	6.6	197
Kuenssber & Knox (1973)	3.0	14668	10.0	48
Lowe (1973)	2.7	31877	5.0	245
Meyer (1973)	2.7	110	18.6	593
Miller & Nevin (1973)	3.8	32227	6.4	110
Monson et al. (1973)	2.4	50591	4.7	306
Niswander & Werteleck (1973)	2.7	347097	4.1	413
Biale et al. (1975)			16.0	56
Knight & Rhind (1975)	3.65	69000	4.3	140
Starreveld-Zimmerman (1975)			7.0	372
Visser et al. (1976)	2.3	9869	3.7	54
Weber (1977)	2.2	5011	4.0	731
Annergers et al. (1978)	3.5	748	8.1	259
Seino & Miyakoshi (1979)			13.7	272
Dietrich et al. (1980)				37
Majewski et al. (1980)			16.0	111
Nakane et al. (1980)			11.5	700
Hiilesmaa et al. (1981)	2.0	5613	7.7	4795
Stanley et al. (1985)	3.4	62265	3.7	244
Beaussart-Defaye et al. (1985)			7.8	295
Rating et al. (1987)	3.7	162	5.3	150

*: Yerby M. (1991)

of them. As seen in table 1, similar research followed in Japan. Including reviews by Taki et al. (1989) and by Takahashi et al. (1990). A prevalence rate for epilepsy of about 1.52% was calculated from research including familial examinations by Friis (1979) and Gadoth et al. (1987). This is higher than the general expectated rate. Further, Friis et al. (1982), who examined the frequency of facial cleft in 3,203 epileptic patients, found that 11 had such a cleft, and together with the results from previous data, concluded that some hereditary link seems to exist between epilepsy and the presence of a facial cleft.

Table 2 illustrates the relationship between epilepsy in parents and malformations in their children. As can be seen from the table, malformations in children, one of whose parents has epilepsy, tend to occur

Table 4. Background factors of maternal epileptics influencing the risk of malformations in their offspring

factors	total sample	non-medicated group	medicated group
Age of first pregnancy	ns	ns	ns
Number of previous pregnancies	ns	ns	ns
Age at current pregnancy	ns	ns	ns
Malformations in previous child	ns	ns	ns
Previous miscarriage or stillbirth	$p<0.01$	ns	$p<0.02$
Presence of maternal malformation	$p<0.001$	ns	$p<0.10$
Characteristics of maternal epilepsy			
Age at onset of fits	ns	ns	ns
Duration of disease	ns	ns	ns
Significant history or duration of treatment	ns	$p<0.10$	ns
Presence of genetic basis of epilepsy	$p<0.02$	$p<0.05$	ns
Organic cause	ns	$p<0.05$	ns
Type of epilepsy (partial vs. generalized)	ns	ns	$p<0.05$
Presence of seizures during pregnancy	ns	ns	ns
Change of frequency of fits during pregnancy	ns	ns	ns
Complication during pregnancy	$p<0.05$	ns	ns
Other than normal delivery	$p<0.01$	ns	$p<0.05$

ns, not significant.

at a higher rate than in the general population. However, this does not lead to the conclusion that epilepsy in one of the parents increases the frequency of malformation in their children, as there was no control group. However, if we make a comparison between the father and mother, evidence suggests that maternal epilepsy is related with a higher frequency than paternal epilepsy. Further, as most mothers were on AED medication, this suggests that the use of AEDs may be related to the occurrence of a malformation.

In relation to the specific relationship between drugs and congenital malformations, it has been shown in animal experiments that phenytoin (PHT), carbamazepine (CBZ) and valproate (VPA) can produce malformed infants, though the content, frequency and severity of the malformation differs depending on the type of animals used.

Research on the appearance of malformations induced by AEDs were initially based on simple case reports (Muller-Kuppers, 1963; Meadow, 1968; Fukushima and Mikawa, 1974; Nakane and Takahashi, 1974), but gradually studies using retrospective and/or prospective data from large numbers of cases have been undertaken (Janz and Fuchs, 1964; German et al., 1970). In recent years, multi-institutional cooperative studies using prospectively collected cases have also been conducted. Table 3 shows the recent data summarized by Yerby (1991).

One of the authors (Y.N.) directed the "Cooperative Study on the Teratogenisity of AED" from 1974 to 1977 with the cooperation of 11 institutions from all over Japan. Some of the findings from the data collected in this study have already been published (Nakane et al., 1980; Nakane 1980, 1982, 1984).

In this study, data were collected for 902 cases of pregnancy in 453 female epileptic patients. Of them,

Table 5. Type and incidence of malformations in two collaborative studies on liveborn children of mothers who took AEDs

	Y.N. study		S.K. study	
	No.	%	No.	%
Cleft lip and/or palate	15	3.14	6	1.69
Cardiovascular malformations	14	2.93	7	1.97
Skeletal malformations	13	2.72	8	2.25
Facial or ear malformations	11	2.30	6	1.69
Gastrointestinal malformations	5	1.04	3	0.84
Urogenital malformations	3	0.63	2	0.56
CNS malformations	1	0.21	0	0
Others	7	1.46	7	1.97
Total	69		39	

657 cases received AED medication during the pregnancy, and 162 received no AED medication. For the remaining 83 cases, information about the drug regime was insufficient. Malformation was observed in 65% of all cases, while the appearance of malformation in live births was only 11.5% (55 cases out of 478) in the AED medicated group and 2.33% (3 cases out of 129) in non-AED medicated group. An analysis of background factors of female epileptic patients, suggested that a history of epilepsy, cause of onset, and type of seizure affected the appearance of malformation (see table 4). However, the frequency of malformation was more likely to depend on the kind of AEDs, dosage, and the pattern of drug combination, than on the influence of maternal factors. In particular, trimethadion had a significant impact. The content and the overall frequency of malformations in 55 live born infants are shown in table 5 (Y.N. study). Further, the malformation rate went up remarkably as the number of AEDs used together increased, although no direct causal relationship was observed between each AED and a specific malformation. On the basis of these results, studies concerned with the prediction of occurrence of malformations and analytic studies using prospectively collected cases were conducted (Nakane et al., 1988). As a result of the malformation syndrome having been identified (German et al., 1970; Diliberti, 1983; Nakane 1987, 1989) and the information about this syndrome becoming widespread, a great change has taken place in the trend of pharmacological treatment of epilepsy. Consequently, a second effort to collect prospective cases of pregnancy in epileptic patients was initiated by one of the authors (S.K.) with the participation of 4 institutions in Japan (Kaneko et al., 1988, 1991).

This time, 379 deliveries, 356 of which involved AED medication during the first trimester and 23 without such medication during the pregnancy, and whose course of pregnancy could be observed prospectively, were examined as subjects. In this paper, results concerned with the comparison of severity of teratogenicity between each AED and between the various combination of AEDs are presented. As in previous investigations, background factors of epileptic patients as well as the nature of prescribed AEDs were examined.

In the non-medicated group, 2 cases with minor anomalies were found, while in the medicated group, various malformations, including some cases with more than one malformation were observed in 36 cases. Malformations observed are presented in table 5 in order to compare them with the results of the previous study (S.K. study). There were 152 cases on a single drug regimen and 204 cases on an AED multiple drug

Table 6. Incidence of congenital malformations

AEDs	monopharmacy		polypharmacy		total	
	normal	malformed	normal	malformed	normal	malformed
PHT	43	1 (2.3)	152	25 (14.1)	195	26 (11.8)
PB	14	0 (0.0)	73	10 (12.0)	87	10 (10.3)
CBZ	5	0 (0.0)	90	17 (15.9)	95	17 (15.2)
VPA	43	3 (10.0)	82	14 (14.6)	125	17 (14.6)
MPB	2	1 (33.3)	13	4 (23.5)	15	5 (25.0)

Parentheses indicate percentages of malformations.

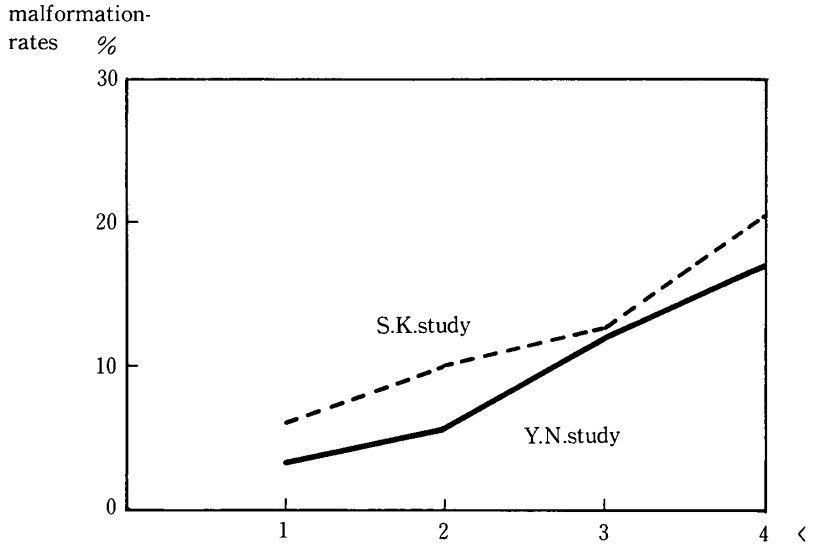

Fig. 4 Distribution of the incidence of malformation plotted by the number of AEDs

regimen, with an overall malformation rate of 10.1%. Viewed from the number of drugs taken, 5.9% of malformations occurred in single drug regimens and 13.3% in multiple drug regimens. The difference in the malformation rate between the two regimen groups was significant.

The malformation rate for each AED used in the medicated group is shown in table 6. In the case of single drug regimens, frequency of malformation was highest for menthylphenobarbitone (MPB) followed by VPA, CBZ, and PHT in this order. No malformation was found for phenobarbitone (PB) and primidone (PRM). Frequency of malformation for MPB was significantly higher than that for PHT and PB. Frequency of malformation increased in multiple drug regimens. The relationship between the frequency of malformation and the number of AEDs given together was also investigated (see figure 4). Results showed a more obvious tendency than in the previous study of the finding that an increase in the number of AEDs administrated is accompanied by a higher frequency of malformations. In relation to PRM and PB, which did not show any malformation when used alone, a high rate of malformation was observed when used

in combination with other drugs.

The rise in the frequency of malformations due to multiple drug regimens and/or to the increase of dose suggests a role played by not only the teratogenicity of the AED itself, but also to the increase of teratogenic metabolites of the AED caused by multiple AED intake. The teratogenic metabolite, epoxide, is produced by PHT, PRM, MPB, CBZ, PB, and is increased by multiple dosage of AEDs. For instance, PHT and VPA accelerate the epoxidation of CBZ, and increase the epoxide body by suppressing the metabolism and catabolism of CBZ. Further, 4-en VPA, the metabolite of VPA which has teratogenic potency, is increased by the combination of CBZ and/or PHT with VPA (Kaneko, 1991). On the other hand, increase of these active metabolites are dependent upon the dosage of each AED (Pissani et al., 1986). Thus, malformations may appear when a large volume of AEDs, even if administrated singly, are given, or when the total amount of AEDs or active metabolites increases because of multiple drug intake. There is a reliable clinical report (Buehler et al., 1990) that the appearance of malformations in the infants of mothers medicated with PHT during pregnancy, is dependent on the activity of epoxide hydrolase in the mothers. This means that, even if an AED is given alone and in a small dosage, epileptic mothers with a low activity of epoxide hydrolase, which is genetically influenced, have a higher risk of bearing malformed infants. As such, it is necessary to measure enzyme activity prior to giving medication. However, as the severity of teratogenicity varies according to each AED, this should be taken into account in the actual administration of AEDs in the clinic. Further, the relationship between folic acid and malformation has long been suspected and it is known that many AEDs, except VPA, reduce the concentration of folic acid. VPA increases metabolite with the teratogenic potency of folic acid.

From our recent study, it was concluded that teratogenicity of MPB and VPA is a major problem in treatment, even if used alone. When used in combination, PHT + PRM + others is dangerous, in addition to VPA + CBZ + other, which has already been described in the literature (Nakane et al., 1988).

Thus, the incidence of malformation may be greatly reduced, in other words, it may be kept as low as that of non-medicated epileptic mothers, by cautiously administering the required minimum medication other than the above mentioned AEDs, singly or in combination, and by supplementing the amount of folic acid before the pregnancy if it is insufficient. Therefore, measures should to be taken to ensure that AEDs are selected carefully, even before pregnancy. Further, if possible, serum concentration of folic acid and the activity of epoxide hydrolase in epileptic women should be determined before they become pregnent (Kaneko et al., 1992).

3) Other Complications in Children

The most important other complications in children include chromosome aberration (a factor that can cause congenital abnormalities), the affect of calcium metabolism, and haemorrhagic disorders. In one study we reported 2 cases (4.2%) out of 48 neonates with the above complications, but no further details are given here as it makes up a different topic.

4) Recommendations Concerning AED Intake during Pregnancy

Based on the research and studies reported in this paper, the Commission on Genetics, Pregnancy, and the Child of the International League Against Epilepsy 1989, made the following recommendation:

Epileptic women, when they become pregnant, should be informed that there is a risk of major malformations and minor anomalies related to their family history, and the type and severity of their epilepsy.

Further, they should be informed that fetuses and neonates may have developmental disorders, and that they might experience various types of convulsion. In particular, VPA, which has the risk of inducing neural tube defects, should be replaced by other AEDs. Heart defects and facial clefts can sometimes result from the use of AEDs, and so ultra-sound examination is recommended to find out if such malformations exist. In the treatment of epilepsy, a single AED regime with the lowest possible dosage is the most desirable medication. Finally, blood concentration of AED should be continuously monitored.

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