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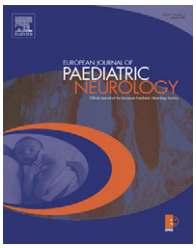
Official Journal of the European Paediatric Neurology Society



Original article

Risk factors associated with the occurrence of frontoethmoidal encephalomeningocele

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ARTICLE INFO

Article history:
Received 30 April 2007
Received in revised form
4 July 2007
Accepted 10 July 2007

Keywords:
Frontoethmoidal encephalomeningocele
Neural tube defect
Thai
Risk factors

ABSTRACT

Objectives: To determine factors associated with the occurrence of frontoethmoidal encephalomeningocele (FEEM), a congenital defect with unique geographical distribution.
Methods: The subjects of this study were 160 unrelated cases of FEEM. Subjects were recruited between 1999 and 2006 from 15 medical centers throughout Thailand. Data obtained from FEEM cases were analyzed and compared with data from 349 cases of oral clefts studied in the same centers and during the same time and those from the general population (GP) taken in 2003.
Results: About 52% of FEEM cases had brain anomalies which were not different among types of FEEM. We found familial aggregation reflected by an increased risk to siblings. All of the FEEM cases were of Thai nationality and came from low socioeconomic status. Seven FEEM cases had amniotic rupture sequences. Compared with oral clefts, advanced maternal age (OR: 1.08, 95% CI: 1.02–1.15) was found to be associated with FEEM. In addition, the interpregnancy interval between the FEEM cases and their previous siblings was significantly longer than that of the oral cleft patients and unaffected sibs (OR: 1.17, 95% CI: 1.06–1.28).
Conclusions: Low socioeconomic status, advanced maternal age, and a long interpregnancy interval may lead to an unfavorable intrauterine environment which, with a certain genetic background such as Thai ethnicity, could contribute to the occurrence of FEEM.

1. Introduction

Frontoethmoidal encephalomeningocele (FEEM) is characterized by a congenital bone defect of the anterior cranium between the frontal and ethmoidal bones with herniation of meninges and brain tissues through the defect.[1] It has been considered a type of neural tube defect (NTD) with the main pathological changes found internally at the foramen cecum and externally at the frontonaso-orbital region.[2] FEEM has been generally categorized based upon clinical and

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Abbreviations: FEEM, frontoethmoidal encephalomeningocele; NTD, neural tube defect; GP, general population; MTHFR, methylenetetrahydrofolate reductase

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doi:10.1016/j.ejpn.2007.07.005

radiological findings into nasofrontal, nasoethmoidal, nasoorbital, and combined type.[3,4] This classification is dependent on the external bone defects. Previous studies did not demonstrate any clinical or etiological significance among different types of FEEM. Associated anomalies are also found with the most common being central nervous system abnormalities.[4] Brain malformations found in FEEM determine the disease outcome. Many infants with FEEM survive with severe disabilities.

FEEM has a unique geographical distribution. It is much more common in Southeast Asia, with an approximate prevalence of 1 in 6000, than in western countries.[5–7] The reason for this is unknown. Recent data from animal and human studies have suggested that neural tube closure is initiated simultaneously in five separate sites which then fuse together.[8,9] It has been shown that NTD in different locations have different incidences, environmental risk factors, genetic susceptibility, and recurrence risks.[7,10–12] Although the factors regulating normal closure and fusion at each site are still unclear, they may include multiple genes or gene–environment interactions. Recent evidences support the role of 677C→T mutation of 5,10-*methylenetetrahydrofolate reductase* (*MTHFR*) in NTD formation at some but not all five closure sites.[11] Defects involving the cervical-lumbar spine, lumbosacral spine, and occipital encephalocele were significantly associated with 677C→T *MTHFR* allele whereas FEEM, anencephaly, exencephaly, and defects confined to the sacrum were not.

Besides being considered as a type of NTD, FEEM has also been hypothesized as having other different pathogenesis. Various theories on the pathogenesis of FEEM have been proposed, one of which is the nonseparation theory.[13] It was initially proposed by Sternberg and further supported by an embryological study in mouse and rat embryos as well as clinical studies in 30 Indonesian patients with FEEM.[13] The pathogenesis of FEEM appears to be related primarily to a disturbance in the separation of neural and surface ectoderm at the site of final closure of the rostral neuropore during the

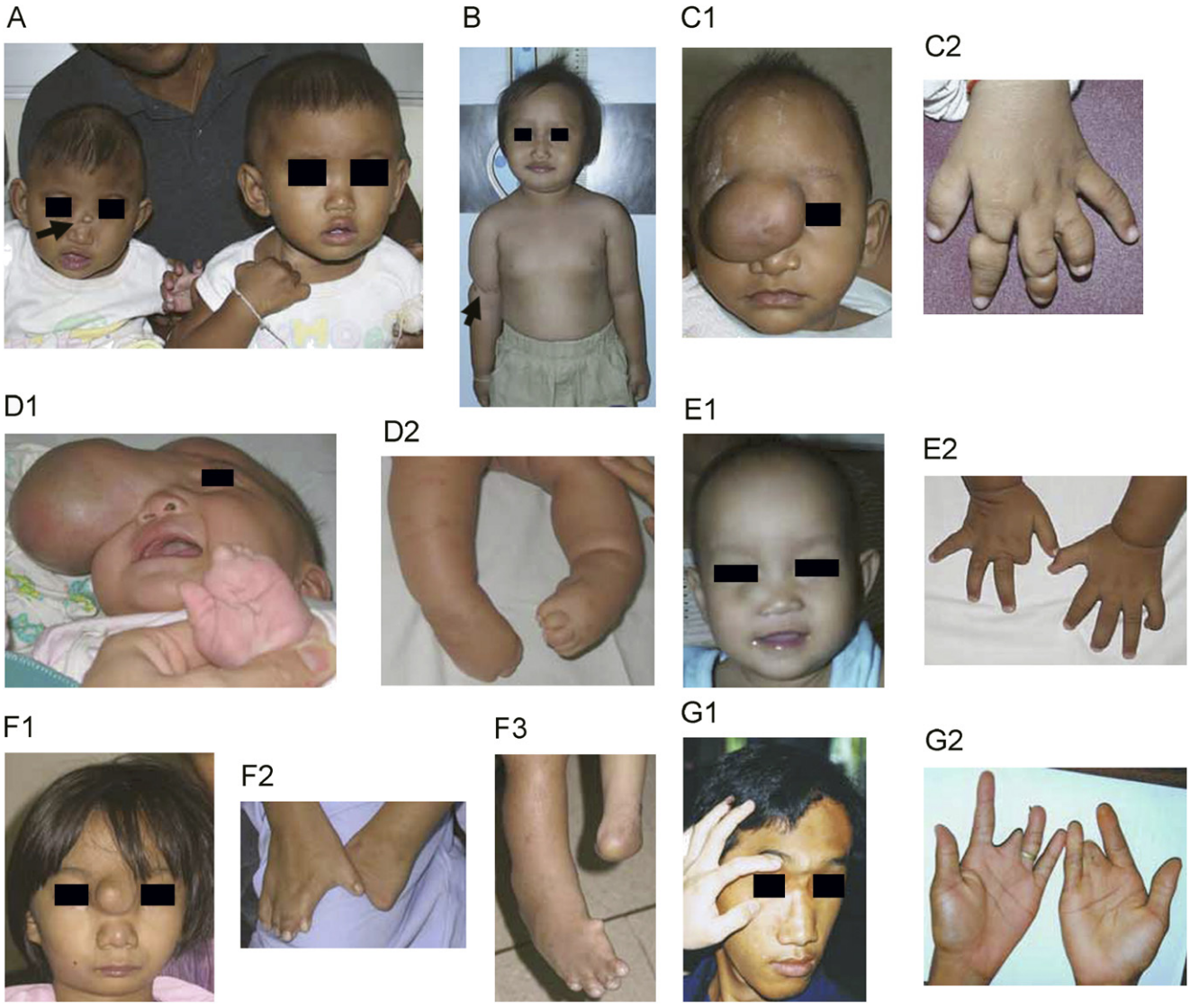

Fig. 1 – Panel A shows a pair of discordant monozygotic twins for FEEM. An arrow indicates a nasal mass representing an encephalomeningocele. Panels B–G show patients with FEEM and amniotic rupture sequences. In panel B, an arrow indicates a constriction ring representing amniotic rupture sequence.

final phase of neurulation. It was postulated that insufficient apoptosis might be responsible for the failure in separation resulting in a midline mesodermal defect. Since the etiology has not been clearly identified, additional analyses of Thai patients with FEEM for associated factors will further elucidate the disease mechanism. We therefore conducted a case control study to determine factors associated with the occurrence risk of delivering an offspring with FEEM.

2. Methods

The subjects of this study were 160 unrelated cases of FEEM with the diagnosis confirmed by computerized tomography of the skull and brain. Subjects were recruited between 1999 and 2006 from 15 medical centers throughout Thailand. All FEEM cases were examined and all the data were reviewed by clinical geneticists (K.S. or V.S.). The study was approved by local Ethics Committees, and written informed consent was obtained from all patients or their parents included in the study. We obtained data regarding demographics, pregnancy, maternal use of medications, tobacco and alcohol use during pregnancy, maternal nutrition, family history and pedigree. The individual's ethnicity was based on the origin of parents. Chromosomal analysis was performed at 400-band resolution. Data from 349 cases of oral clefts studied in the same centers and at the same time and those of the Thai general population (GP) in the year 2003, obtained from Thai Census Bureau, National Statistical Office, Thailand, were used for comparison. Even though oral clefts are multifactorial and have etiological heterogeneity, FEEM and oral clefts are two distinct entities without any causal relationship having been demonstrated. We also used data from GP as a control for this study assuming that FEEM has a low incidence and occurrence of FEEM cases would have a negligible effect on the GP structure.

Statistical analyses included examination of distribution of characteristics of FEEM patients and their mothers, and estimation of unadjusted and multivariate-adjusted odds ratio (OR) with 95% confidence interval (CI). All data were analyzed using SPSS (version 11.5, SPSS Inc.) We made univariate comparisons of dichotomous data by using the χ^2 test. p value <0.05 is considered statistically significant. Multivariate-adjusted ORs were derived using a logistic regression model, adjusted for the following factors: gender, maternal age, birth order and interpregnancy interval. Each independent variable was added individually to calculate adjusted ORs for the disease outcome. Significance was judged at $p<0.05$. The interpregnancy interval was described with median and interquartile range due to non-parametric distribution. Significance of difference in interpregnancy interval between two different groups was determined using the Mann–Whitney's U-test.

Table 1 – Types of FEEM and associated brain anomalies among cases with FEEM

External bone defect	No. of cases (%)	No. of cases with associated brain anomalies (%)
NF type	23 (14.4)	12 (52.2)
NE type	55 (34.4)	27 (49.1)
NO type	15 (9.4)	9 (60)
Combined type (NE+NO)	67 (41.8)	35 (52.2)
Total	160	83 (51.9)
Brain anomalies[a]		No. of cases (%)
Dysplastic ventriculomegaly		54 (33.8)
Dysgenesis of corpus callosum		37 (23.1)
Absent septum pellucidum		14 (8.8)
Arachnoid cyst		22 (13.8)
Porencephaly		3 (1.9)
Schizencephaly		7 (4.4)
Holoprosencephaly		2 (1.3)

[a] Several forms of brain anomalies can be found in one FEEM patient.

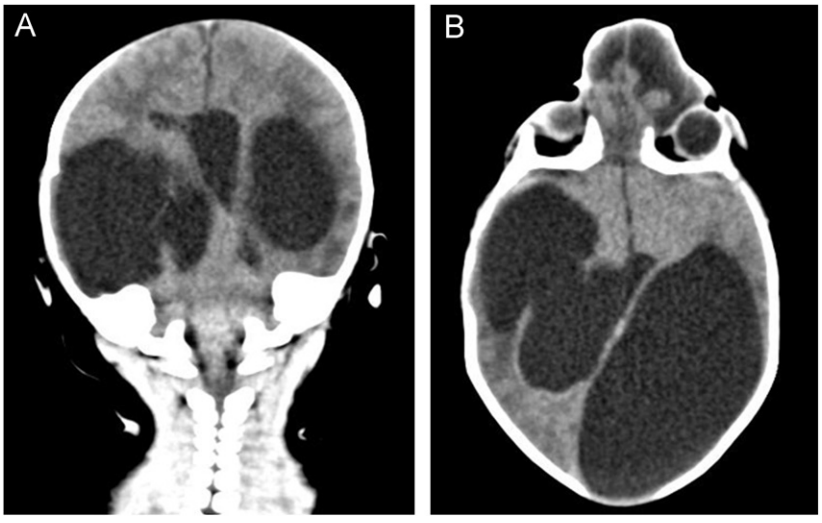

Fig. 2 – The brain CT scan of a patient with FEEM showing dysplastic ventriculomegaly: (A) the coronal plane and (B) the axial plane.

3. Results

Of 160 FEEM patients, 158 cases were sporadic and 2 reported affected siblings. There were a total of 310 siblings from 160 FEEM families. With the prevalence of FEEM in the GP being 1 in 6000,[5–7] the risk to siblings (λ_{sib}) was therefore equal to 38.7. Two of our FEEM patients had unaffected monozygotic twins (zygosity of a pair was determined by molecular studies using 13 microsatellites) (Fig. 1A). The age of patients at the time of referring to our centers ranged from 1 day to 42 years old. Considering external bone defects, the combined type had the highest occurrence (41.8%, Table 1). Congenital brain anomalies were detected in 83 patients (51.9%) and the differences in frequency found among different types of FEEM were not statistically significant (Table 1). There were various forms of brain anomalies found in FEEM with the most frequent being dysplastic ventriculomegaly (Table 1, Fig. 2). Amniotic rupture sequences were found in 7 out of the 160 FEEM patients (Fig. 1B–G, the photograph of the 7th patient not shown).

While at least 10% of Thai population are Chinese,[14] all our FEEM cases identified themselves as ethnic Thai. All of our FEEM cases were from low-income families with parents who were blue-collar workers. All mothers of FEEM affected patients lacked periconceptional supplementation of folic acid, similar to the mothers of patients with oral clefts. All the mothers did not smoke nor take significant amount of alcohol.

Compared to GP and oral cleft patients, advanced maternal age was associated with FEEM. In addition, interpregnancy interval was significantly longer in FEEM cases when compared to that of oral cleft patients (Table 2 and Figs. 3 and 4). A high percentage of FEEM cases were born at the high birth rank. However, it was not statistically significant after adjusted for other variables. Of the 80 FEEM patients whose samples were available for chromosomal analysis, all had normal karyotypes.

4. Discussion

We found familial aggregation reflected by an increased risk to siblings. This agrees with previous studies.[6,7] The reason for this could be sharing of genes and/or environments. While at least 10% of the populations of Thailand are Chinese,[14] all our FEEM cases identified themselves as ethnic Thai. This finding agrees with a previous observation that all FEEM patients in Malaysia were Malay although there were three major ethnic groups (Malay, Chinese and Indian) in Malaysia.[12] The high prevalence of FEEM in these particular ethnicities also suggests that genetic factors may be associated with the development of FEEM. The findings that most of them were sporadic and two of the FEEM patients had unaffected monozygotic twins suggest that FEEM is unlikely to be inherited in a Mendelian fashion. In addition, all of our patients sent for chromosomal analysis had normal karyotypes, indicating that FEEM is not a chromosomal disorder caused by gross rearrangements. However, submicroscopic genomic rearrangement leading to susceptibility to FEEM in some population cannot be excluded as many submicroscopic genomic rearrangements have been found to be associated with a wide spectrum of disease traits. High-resolution genome analysis may identify the susceptibility genes previously intractable to conventional genetic analyses.

Table 2 – Characteristics of patients with FEEM, oral clefts and the general Thai population (GP)

	FEEM ($N = 160$)	Oral clefts[a] ($N = 349$)	GP[b] ($N = 803,157$)
Sex			
Male (%)	80 (50.0)	207 (59.3)	412,840 (51.4)
Female (%)	80 (50.0)	142 (40.7)	390,317 (48.6)
p Value	0.50	<0.003	Ref
Maternal age (years)[c]			
<35 (%)	88 (61.1)	306 (87.7)	708778 (87.8)
≥ 35 (%)	56 (38.9)	43 (12.3)	98413 (12.2)
Unadjusted OR	4.53	1.01	Ref
(95% CI)	(2.78–7.39)	(0.73–1.41)	
Adjusted OR	1.09	Ref	N/A
(95% CI)	(1.04–1.15)		
Birth order			
1st–3rd (%)	115 (71.8)	306 (87.9)	767206 (94.5)
$\geq$4th (%)	45 (28.2)	43 (12.1)	44669 (5.5)
Unadjusted OR	2.78	2.41	Ref
(95% CI)	(1.70–4.58)	(1.73–3.36)	
Adjusted OR	1.07	Ref	N/A
(95% CI)	(0.84–1.37)		
Interpregnancy interval (years)[d]			
Between the index case and the preceding unaffected sibling	7, 4–11 (a) ($n = 80$)	4, 2–7 (b) ($n = 178$)	N/A
Between two unaffected siblings	3, 2–4 (c) ($n = 109$)	3, 2–4 (d) ($n = 296$)	N/A
p Value	<0.001[e], <0.001[f]	N/A	N/A
Adjusted OR	1.15	Ref	N/A
(95% CI)	(1.05–1.26)		
Amnion rupture sequence (%)	7 (4.1)	1 (0.3)	N/A

[a] The patients with oral clefts include individuals with either cleft lip or cleft palate or both. We also compared the data from FEEM cases with those from patients affected with cleft lip with or without cleft palate and patients with cleft palate alone. The results were similar to the study of cases with FEEM and oral clefts. Hence only the data from patients with oral clefts are presented.
[b] Data from year 2003, Thai Census Bureau, National Statistical Office, Thailand (http://web.nso.go.th). The total number of GP is not similar in each category due to non-included unknown data.
[c] There were 144 FEEM cases with maternal age data available.
[d] The interpregnancy interval is defined as the period between two consecutive deliveries. It was calculated in months and converted into years. It was described with median and interquartile range.
[e] Comparison between cells (a) and (c) using the Mann–Whitney's U-test.
[f] Comparison between cells (a) and (b) using the Mann–Whitney's U-test.

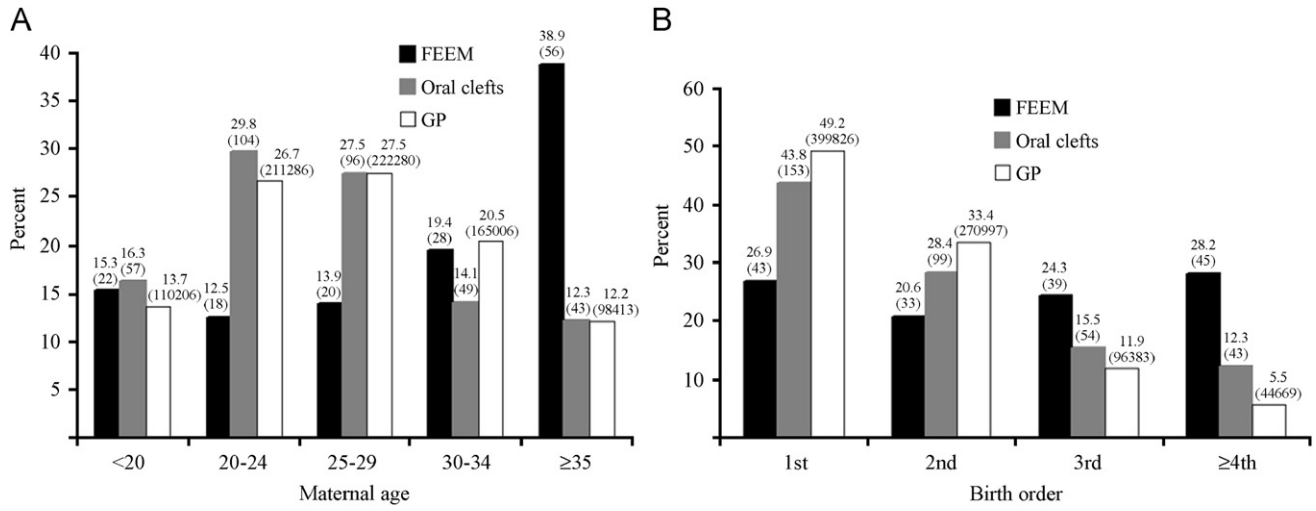

Fig. 3 – Risk factors associated with FEEM occurrence. Graphs A and B represent percentages of individuals from each category (FEEM, oral clefts, general population) in relation to maternal age and birth order, respectively. The number in parenthesis represents total numbers of individuals in each group.

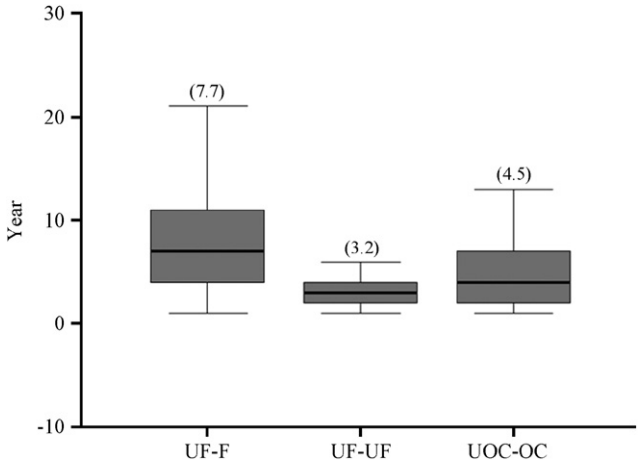

Fig. 4 – Comparison of interpregnancy interval among the preceding unaffected sibling and the proband with FEEM (UF-F), the 2 preceding unaffected siblings of FEEM (UF-UF) and the preceding unaffected sibling and the proband with oral clefts (UOC-OC). The number in parentheses represents a median with interquartile range.

It is most likely that interaction of genes and environment involves in development of FEEM.

All of our FEEM cases were from low-income families with parents identifying themselves as blue-collar workers. This finding is unlikely due to an ascertainment bias because our Craniofacial Center has been one of a few centers in Thailand capable of operational correction of the defect and has served many patients with other anomalies of various ethnicities and all socioeconomic classes. In addition, our patients with oral clefts were from families of different ethnicities and all socioeconomic classes. Association with low socioeconomic status, similar to a previous observation,[7] suggests a significant role for environmental factors in FEEM. In fact, we have observed the lower incidence of FEEM (3 out of 107,889 births or 1 in 35,963) in our center, King Chulalongkorn Memorial Hospital, collected during the 9-year period of 1994–2002 (data unpublished), compared to 1 in 6,045 (7 out of 42,315) studied in the same hospital during 1962 and 1966.[5] Studies of incidences of FEEM in rural communities of Thailand during 1960s to early 1970s showed similar incidences of 1 in 3500 to 1 in 7428.[5,6] Higher socioeconomic status of the 1990s compared to that in 1960s may be a part in decreasing the incidence of FEEM.

The percentage of Thai expectant mothers taking folic acid periconceptionally has been exceptionally low as demonstrated by our recent study.[15] Only 0.3% (1/383) reported taking folic acid before pregnancy. None of the mothers with FEEM affected children took any folic acid before conception, similar to the mothers of patients with oral clefts in our studies. While association between polymorphisms in *MTHFR* and some locations of NTD have been established, a previous study failed to show an association between polymorphisms in the *MTHFR* gene and FEEM.[5] This suggests that FEEM and NTD in other locations may have different pathogenesis. Alternatively, FEEM may not be a type of NTD as proposed by some recent studies showing that FEEM appears to be related to a disturbance in the separation of neural and surface ectoderm just after closure of the neural folds, which might be caused by an insufficient occurrence of apoptosis.[13]

The interpregnancy interval was found to be longer in FEEM cases in a previous study.[7] However, it has been inconclusive since other confounders were not included in the analysis. Adjusting for other demographic variables, this study showed that advanced maternal age, and long interpregnancy interval were associated with FEEM when compared to oral cleft patients. This suggests an unfavorable intrauterine environment for fetal growth including the development of the anterior part of the cranium in individuals with genetic predisposition to FEEM. It has been hypothesized that the growth-supporting capacities of the uterus, such as increased uterine blood flow and other physiologic and anatomical

adaptations, gradually decline if no fetus is conceived for a long time.[16] The unfavorable intrauterine environment has been suggested to contribute to amniotic rupture sequences,[17] which were found in seven out of our 160 FEEM patients.

Our study supports that genetic and environmental factors have a role in the development of FEEM. Even though the susceptibity genes have not been identified, studies about its pathogenesis might give some clues to the candidate genes. According to the nonseparation theory, insufficient apoptosis might be one of the underlying pathogenic mechanisms. The genetic factors contributing to FEEM in Thai patients might include the genes involved in the apoptosis pathway. Further analyses of Thai patients affected with FEEM will undoubtedly contribute to the understanding of this intriguing congenital anomaly.

In conclusion, our study comprises the largest group of imaging-confirmed FEEM patients reported. Low socioeconomic status, advanced maternal age, and a long interpregnancy interval may lead to an unfavorable intrauterine environment which, under a certain genetic background including Thai ethnicity, could contribute to the occurrence of FEEM. Primary care providers or providers of reproductive health care could counsel women of reproductive ages especially those in high-risk ethnic groups about the association between the potential risk factors such as long interpregnancy interval, extreme maternal age and the occurrence of FEEM. Our findings suggest a further study to explore these potential factors in various high-risk ethnic groups and a possible strategy to reduce the incidence of FEEM.

Conflict of interest

We have no conflicts of interest.

Acknowledgments

We wish to thank the medical staff of the Thai Red Cross and the Provincial Hospitals of Nakornratchaseema, Srakaew, Uthaithanee, Nan, Maehongsorn, Trang, Prachinburi, Kalasin, Nongkhai, Mahasarakam, Chaiyapoom, Leoy, Yasothorn and Mukdaharn, for the excellent care of their patients. We are grateful to Professor Henry Wilde of the Division of Research Affairs, for reviewing the manuscript. This study was supported by the Ratchadapiseksompotch Fund, Faculty of Medicine, the Research Unit Grant from Chulalongkorn University, the National Center for Genetic Engineering and Biotechnology, and the Thailand Research Fund.

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