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Epidemiology of frontoethmoidal encephalomeningocoele in Burma

AUNG THU[1] AND HTA KYU[2]

From the Department of Anatomy,[1] Institute of Medicine 1, and the Department of Pathology,[2] Institute of Medicine 2, Rangoon, Burma

I An outpatient study

HTA KYU AND AUNG THU

SUMMARY One hundred and thirty nine patients suffering from encephalomeningocoele and myelomeningocoele who had attended the neurosurgical outpatients department of the Rangoon People's Hospital were interviewed. A predominance of frontal encephalomeningocoele was found; a low proportion of these patients had been conceived in the cold season and an increased interval separated the index patients from the previous full term pregnancy of their mothers; no first degree relatives were affected. It is suggested that an environmental factor is implicated in the developmental aetiology.

Suwanwela reported variations in the geographical distribution of various defects of neural tube closure.[1] He reported that spinal myelomeningocoeles (SMM) and occipital encephalomeningocoeles (OEM) were common while frontoethmoidal encephalomeningocoeles (FEEM) were rare in England and Wales, Germany, United States, Australia, Nigeria, and India; conversely FEEMs were more common in Thailand, Malaysia, Indonesia, and Russia (table 1). Our previous experience in neurosurgical units in Burma suggested that the proportion of FEEMs in Burma might be as high as that in Thailand. Consequently we decided to study, first of all, patients with OEM and FEEM attending the neurosurgical outpatients clinics of the Rangoon People's General Hospital over a period of 18 months from August 1979 to January 1981. We planned to determine the proportion of FEEMs and to identify associated factors and possible aetiological agents.

Subjects and methods

We designed a questionnaire concerning the personal history of the patient, the obstetric history of the mother, the time and place of conception, the mother's place of residence during the first trimester of pregnancy, the marital history of food and drugs taken during the pregnancy, and the prevalence of the defect among relatives. In each case the parents or close relative who accompanied the patient were interviewed. As these patients had been examined only as outpatients and had not undergone surgery it was not possible to exclude meningocoele without herniation of the brain or spinal cord.

Results

Number of patients—In the study period of 18 months 139 patients with meningomyocoele were seen; 16 of these had SMM, nine had OEM, and 114 had FEEM. Thus the ratio of FEEM to OEM was 12·7 to 1·0. Of the 114 patients with FEEM, 14 had clinically detected hydrocephalus.

Age—The oldest patient was 34 but 73 (64%) of the patients with FEEM were under 2 years.

Sex—There were 63 males and 51 females which was a male/female sex ratio of 1·23 similar to that reported by Suwansela and Hongsaprabhas in Thailand of 1·27.[2]

Race and religion—All major ethnic groups were represented, and the distribution among the three major religious groups (Buddists, Christians, and Muslims) were similar to the national proportions with no suggestion of any ethnic or religious predilection. There were a few patients among the

Table 1 *Ratio of occipital encephalomeningocoele (OEM) to frontoethmoidal encephalomeningocoele (FEEM) in various countries as reported by Suwanwela[1] compared with the present study*

Country	*Author*	*OEM*	*FEEM*	*Ratio*
England	Lorber (1961)	15	1	15.0:1
Germany	Gerlach and Jensen (1960)	79	36	2.2:1
United States	Mealey *et al* (1970)	55	8	6.9:1
Australia	Barrow and Simpson (1966)	11	2	5.5:1
Morocco	Acquaviva *et al* (1966)	59	37	1.6:1
Nigeria	Odeku (1967)	29	7	4.1:1
S Africa	Lipschits *et al* (1969)	17	15	1.1:1
India	Tandon (1970)	24	11	2.1:1
Russia	Sokolow (1939)	20	119	1.0:5.9
Thailand	Suwanwela (1972)	11	105	1.0:9.5
Burma	Present series	9	114	1.0:12.7

OEM = Occipital encephalomeningocoeles.
FEEM = Frontoethmoidal encephalomeningocoeles.

Chinese and Indian immigrants and in the children of marriages between these immigrants and the local ethnic groups.

Socioeconomic status—We classified the patients with FEEM according to their father's occupation. Since these patients had originated from all parts of the country we compared them with the proportions in the total working population. There was a higher proportion of children of professional, managerial, and clerical workers which may be a consequence of these groups making greater use of the available health services.

Parental age—There was no association with either maternal or paternal age (table 2). The mean maternal age was 28·9 and the mean paternal age 32·0 at the time of birth. The age specific fertility rate for women in Burma was highest in the 25–29 age group.

Table 2 *Age of parents at time of birth of patients with frontoethmoidal encephalomeningocoeles*

	No of patients	
Age of parents	*Mother*	*Father*
<20	11	2
20–24	32	26
25–29	24	24
30–34	14	18
35–39	19	18
40–44	14	16
45–49	—	9
50–54	—	1
All ages	114	114

Consanguinity—There did not seem to be any significant increase in consanguinous marriages among these parents compared with the general pattern in Burma.

Birth order—There was neither an excess of firstborn nor any association with high parity nor any maternal age or birth rank effect such as has been reported in other neural tube closure defects.[3,4]

Seasons of the year—The time of conception was calculated from the date of birth and we compared this with the month and season of conception of 570 children attending a rural primary school in Zigon (table 3). We have since realised that the season of conception of siblings of the index cases would have been a better comparison group. The season of conception of the subjects with FEEM showed a significantly reduced rate ($<0·01$) in the cold season compared with the Zigon children.

Mean interval between full term deliveries—The mean interval separating the index patient and the preceding normal full term delivery was compared with the mean interval between the preceeding two normal full term deliveries in the same mother (table 4). Of the 114 patients, 20 were primiparas, and 15 patients lacked evidence of the time of conception of their siblings, leaving 79 subjects in this exercise. The interval separating the index cases and the preceding full term delivery was significantly longer than that between the preceding two normal full term deliveries ($p<0·01$).

Affected siblings—None of the 354 live births preceding or following the index cases were found to have the defect. The male cotwin of an affected

Table 3 *Proportion of conceptions by month for patients with frontoethmoidal encephalomeningocoeles (FEEH) and for a comparative group of children in a rural school in 1980*

Time of conception		*Patients with FEEM*		*Rural schoolchildren*	
Season	*Month*	*Month (%)*	*Season (%)*	*Month (%)*	*Season (%)*
	Feb	8·8		8·3	
	Mar	10·5		11·1	
Hot season			35·1		33·2
	April	5·3		6·7	
	May	10·5		7·1	
	June	7·0		9·8	
	July	8·8		10·2	
Rainy season			43·8		37·1
	Aug	15·7		9·1	
	Sept	12·3		7·9	
	Oct	6·1		9·5	
	Nov	3·5		6·3	
Cold season			21·1		29·7
	Dec	4·4		7·2	
	Jan	7·0		6·7	

Table 4 *Mean duration in months between two preceeding normal full term deliveries and betwen an index case and a preceding normal full term sibling*

Groups studied	*No of pairs*	*Mean duration (months)*	*SD (months)*
Between 2 preceding normal full term siblings	145	31·9	17·7
Between index case and preceding normal sibling	79	45·5	13·1

Mean difference is statistically significant ($t = 6·5$ $p<0·001$).

female patient was normal. The spontaneous abortion rate in the index families was 6·3% and the stillbirth rate was 1·1%. The abortion rate recorded for all deliveries in hospitals is 10·2% and in the community this would be expected to be higher.

Affected parents and relatives—None of the parents was affected. None of the patients had had their own child. A paternal uncle of a patient was reported to be suffering from the defect as also were a paternal aunt, a paternal great uncle, and a maternal cousin of three other patients.

Discussion

This study is essentially one of patients attending the neurosurgical units of a large referral hospital and consequently is subject to all the biases inherent in a hospital study. The age distribution, the sex ratio, and the proportions of the ethnic, religious, and economic groups may differ from that found in cases in the community. Many patients may live far away, and there will be social, cultural and educational barriers to attending a hospital; some patients may have died before they could be seen; a higher proportion of female patients may be brought for treatment for cosmetic reasons. Nevertheless, it is possible to draw some general conclusions.

This study provides clear evidence that in Burma, as reported in Thailand, anterior encephalomeningocoeles are much commoner than other neural tube defects associated with survival. It also shows that there is no familial association with the defect. There were no two affected persons in the same index family; all parents of the affected patients were normal; the only dizygotic twin was unaffected. Race, religion, and parental age do not appear to influence the condition, although bias in the sample may obscure any such association. There was no preponderance of one sex, and no association was found with maternal age, parity, or birth rank.

This lack of epidemiological association is in pronounced contrast to the associations found with other neural tube closure defects such as anencephaly and spina bifida. In these latter conditions Williamson recorded a female preponderance,[4] Fedrick noted variations in maternal age and birth rank,[5] and Yen and MacMahon showed a 4·6% risk in siblings born after a prior index case.[6] The absence of the defect in parents and siblings and the low prevalence in distant relatives of an index case could well support Suwanwela's hypothesis[1] that genetic mechanisms do not play a primary part in the aetiology of this condition. Flatz and his colleagues, however, suggested that there might be inheritance of a dominant gene with low penetrance or a multifactorial pattern of inheritance.[7]

We considered that the absence of an association with ethnic, religious, and social factors would appear to exclude a cultural influence in the aetiology. Simple vitamin deficiency as suggested by Suwanwela seems improbable,[1] as about half the mothers in this study had received vitamin supplements during pregnancy, although this may have been received after closure of the neural tube. The low proportion of cases conceived during the cold season might suggest that temperature or other environmental factors associated with season of the year might have a part to play.

An important observation is that there is an increased interval between the birth of the index case and the previous full term delivery which might indicate an unfavourable uterine environment for the fertilised ovum. De Klerk has suggested that adhesions between the neuroectoderm and the surface ectoderm may prevent the normal ingrowth of mesoderm to form a normal skull.[8]

We conclude that at present no satisfactory explanation for these defects can be given but it would be reasonable to assume a developmental aetiology associated with specific environmental factors rather than a genetic cause. We decided to embark upon community studies of the condition.

II A community survey

AUNG THU AND HTA KYU

SUMMARY A postal questionnaire was sent to all hospitals and health centres in Burma and to many local authorities asking for details of known cases of frontoethmoidal encephalomeningocoele. Responses were obtained covering a population of 2·65m in which 389 cases were identified, giving a minimum prevalence of 15 per 100 000 persons. Questionnaires and personal interviews with subjects showed that their families were largely rural and either unemployed or working as peasants in rice paddies. No first degree relative of a subject was affected; a higher proportion than expected was conceived in the rainy season. This suggests that the aetiology of the condition is unlikely to be genetically determined but may be associated with maternal diet before conception or during early pregnancy

In the first part of this series of papers we showed that frontal encephalomeningocoeles are a considerable problem in Burma. Little is known of the aetiology of the condition, but we suggested that a developmental aetiology associated with environmental factors was more likely to be a causal factor than were genetic factors. The present paper reports the results of a nationwide survey that was undertaken to obtain more information in this problem.

Subjects and methods

We considered that since frontal encephalomeningocoele is not a seriously debilitating nor a disabling condition only a small proportion of cases would attend hospital or come to the attention of medical personnel. Consequently we planned to obtain information from civil authorities as well as from hospitals. We prepared letters describing the condition and enclosed a photographic poster with a page of instructions. If cases were known to occur in the district we asked for the name and address of all subjects their age, sex, ethnic group, and the occupation of the father and the number of the population in the relevant district. If no case was known only the question relating to the total population was to be answered, together with a signed statement that no case was known.

Letters were sent to every hospital and health centre in the country, to all the chairmen of the township peoples's councils in all the 314 townships, and to a random sample of 314 village tracts.

In sampling the village tracts a single township was chosen at random from each of the 14 states and divisions, then every village in that township was selected and a letter sent to the chairman of the village tracts people's council. About three months after the despatch of the letters the replies stopped coming in, so we carried out a preliminary analysis of the response rates and the prevalence reported. The disease was found to be highly prevalent in certain parts of the country and rare or absent in others. We decided to take further samples to confirm or disprove this apparent geographical distribution, so we selected the Tenasserium Division where no case had been reported and the more densely populated Pegu Division which had reported the most cases. We then wrote to every village tract chairman in Tenasserim and to a random half of those in Pegu.

By these methods we obtained the names and addresses of 389 subjects who were alleged to be affected. We now posted a questionnaire containing 12 points to the township medical officers of the townships in which the subjects resided and asked them to arrange for the subjects to be examined and for the questionnaire to be completed and returned to us. We also gave the questionnaire to teams of final year medical students from the two institutes of medicine in Rangoon who used them during field trips which covered urban and rural areas in 61

townships. After deleting replicates 194 questionnaires were returned.

Results

Response—We sent out 2108 letters and received 487 replies, a response rate of 23·1%; the population covered by these responses was 2 658 900, which is about 8% of the population of Burma. The 389 cases reported in this population gave a prevalence of 14·6 per 100 000 persons. Table 5 shows the pattern of response and the estimated prevalence for each of the 14 states or divisions. The response rate varied from about 40% in Chin, Kachin, and Kayah to only 3% in Karen. The prevalence varied from no case at all in three divisions to 18 per 100 000 persons in Pegu.

Sex—There were 201 males and 188 females giving a male:female ratio of 1·07 which does not differ significantly from the national ratio at birth.

Age—Table 6 gives the age distribution. The youngest subject was 3 days old, the oldest 90 years, and three others were in their 80s.

Ethnic distribution—Both parents of 313 subjects were Burmans and 13 others had one Burman parent. There were 20 Arakanese, 16 Shans, 12 Karens, eight Chins, three Danu, and one each of Kachin, Kayah, Pa-Aint, and Chinese. There was an absence of Mons, who are a major ethnic group, but the response rate from the Mon States was only 3·5%.

Socioeconomic status—We classified the father's occupation using the Burma Standard Classification of Occupation and in table 7 have compared this with the national pattern. The condition is more prevalent among the families of agricultural workers and of those not classified by occupation (the unemployed) and it was less common among professional and clerical workers and craftsmen.

Rural/urban ratio—Only nine of the 389 reported cases were resident in urban areas whereas about 24% of the national population are urban.

Family history—There was never more than one case in a sibship in all 389 cases that were tested by comparing the subject's name, the father's name, and the addresses. In the 195 subjects who replied to the detailed questionnaire, although there were families with up to 14 siblings, only nine subjects had no siblings yet there were no familial cases. Parents of subjects were always unaffected, and of the 23 cases who had married, 21 had had 80 children, none of whom was affected or had any other congenital malformation.

Season of conception—In 145 cases the month of conception of the subject could be calculated and of these, 106 (73%) were born in the rainy season June to September. This is in complete contrast to the month of conception of children attending a rural school or of 2170 babies born in an urban area (table 8).

Discussion

The limitations of a postal survey are obvious, especially with a low response rate of 23%. But we have some justification for believing that all cases reported were genuine and that therefore we may accept the calculated prevalence rates as minimum rates. Local health personnel with a definite ability to recognise the condition and to differentiate it from

Table 5 *Letter and replies and prevalence of cases per 100 000 population covered by state or division*

State or division	*Letter posted*	*Replies received*	*Population covered (1000s)*	*Population as of % of total*	*Cases reported*	*Cases per 100 000*
Arakan	71	23	93	4·8	16	17
Chin	45	19	19	5·1	2	10
Kachin	51	19	49	5·5	0	–
Karen	30	1	31	3·1	0	–
Kayah	29	12	17	11·8	2	12
Mon	47	7	96	6·3	0	–
Shan	132	35	111	3·0	12	11
Irrawaddy	70	18	188	4·0	23	12
Magwe	77	26	192	6·3	27	14
Mandalay	80	20	76	1·8	7	9
Pegu	1031	198	1058	29·0	187	18
Rangoon	87	16	78	2·1	13	17
Sagaing	109	33	306	8·7	44	14
Tenasserim	241	60	343	41·2	56	16
Burma	2108	487	2657	8·0	389	15

Table 6 *Age distribution of cases in the national survey of Burma compared with the age distribution of the total population*

Age group	Cases		Burma
	No	%	(%)
<4	89	23	15
5–9	72	19	14
10–14	61	16	13
15–19	44	11	10
20–24	32	8	8
25–44	63	17	23
45–64	17	4	13
65–74	3	1	3
≥75	4	1	1
All ages	385	100	100

The wide divergences among different areas of the country and the prevalence in almost all ethnic groups support the hypothesis that environmental and geographical factors play an important part.[1 8] Association with socioeconomic status suggests that maternal nutrition might be relevant. Considering the number of cases among groups in which mothers could be expected to have access to a full nutritious diet, however, we suspect that the noxious agent is a component of food eaten by the mother during a critical stage of pregnancy rather than a deficiency. There seem to be two clues to this agent. Firstly, it is one that is predominant in a rural peasant environment as suggested by the urban/rural ratio and by the high prevalence among rice farmers. The

Table 7 *Association with socioeconomic status*

Occupation*	No of cases	Percentage distribution of total cases	Percentage distribution of general population
Professional and technical workers	7	1·9	2·2
Administrative, executive, and managerial workers	2	0·5	0·4
Clerical workers	5	1·3	2·3
Sales workers	16	4·3	8·5
Agriculture, animal husbandry, forests, and fisheries workers and hunters	292†	78·3	63·3
Miners and quarry workers	1	0·3	0·2
Transport and communication workers	3	0·8	0·9
Craftsmen, production workers, and labourers not elsewhere classified	23	6·2	20·7
Service, sports, and recreation workers	3	0·8	0·6
Workers not classifiable by occupation	14	3·7	0·3
Armed forces	7	1·9	0·9
	373‡	100·0	100·0

*Father's occupation according to Burma Standard Classification of Occupation.
†Of 292 cases, 273 were rice paddy farmers.
‡Out of 389 cases, 16 did not disclose father's occupation before his death.

other pathological conditions identified and confirmed 275 cases; 85 were seen by village chairmen or headmen who, though not medically trained, could be relied on to recognise such a conspicuous lesion as a frontal encephalocoele after they had received our poster and instructions; and final year medical students on a field trip confirmed 29 cases and did not find any cases misdiagnosed although they found 16 additional cases.

In a similar study in Thailand Flatz and Sukthomya found 14 cases with no familial cases but as none of their subjects had had children they emphasised the importance of studies that could examine the offspring.[7] Suwanwela who found a similar lack of familial cases and a discordant affection in a pair of identical twins concluded that a genetic mechanism could not be the primary cause.[1] We found no familial case but we had no twin. We had, however, 80 unaffected children of known subjects which would encourage us to support the conclusion that genetic mechanisms do not play a primary part in the causation of the disease.

second is the apparent relation to humidity at the time of conception. This recalls the fungal hypothesis for the causation of neural tube defects.[9] As fungi need 90–95% humidity to produce toxins[10] this could occur only during the heavy monsoon months, which is the season of conception of a considerable proportion of the cases.

The presence of four people aged over 80 would exculpate every drug in the Western pharmacopoeia from playing a part in the aetiology of the condition.

Table 8 *Proportion of births by season of conception (1) 145 cases with frontoethmoidal encephalomeningocoeles, (2) 569 rural children, and (3) 2170 urban children*

Season	FEEM (%)	Rural (%)	Urban (%)
Hot Feb–May	19	34	34
Wet June–Sept	73	37	30
Cold Oct–Jan	8	29	36

This community study confirms our outpatient study that frontal encephalocoeles have a high prevalence in Burma, that the aetiology is unlikely to be genetic, but that there may be a seasonally determined environmental factor. In contrast with that study, however, the community study implicates the peasant community rather than the urban population and a lower social stratum rather than a higher one.

We proposed to continue our research by investigating the detailed genetic relations within the families of the subjects.

III Family studies

AUNG THU

SUMMARY Thirty five cases of frontal encephalocoele were personally seen and examined at their homes. Of these, 19 had from one to eight children. Three had grandchildren. All available relatives were also examined. None of the progeny or other relatives of the subjects were found to be affected with the condition.

Family studies of major congenital malformations of the nervous system have been done to discover a genetic pattern of inheritance.[5] Flatz and Sukthomya studied 14 families that had a member affected with frontal encephalocoele.[7] None of those affected had children, and it was mentioned that data concerning the offspring of affected people would be helpful in testing polygenic inheritance or other genetical hypotheses. This study is a personal verification of some data obtained from two previous studies of frontal encephalocoele in Burma (parts I and II above). Our epidemiological survey of the condition in Burma discovered 389 cases and a follow up questionnaire survey showed that among 195 subjects, 23 were married and 21 had children. A tour was made with the primary purpose of examining their offspring.

Material and methods

I visited 46 villages in 27 townships of the country in which 19 of the 21 subjects with children were found and examined. A considerable distance had to be travelled over a vast area and in the process 16 additional subjects without progeny were also seen. All 35 were clinically examined and confirmed as suffering from frontal encephalocoele. Three who had previously been reported by headmen as frontal encephalocoele were found to have been eroneously reported and were excluded from the study. All available relatives of those affected were examined for "formes frustes," presence of any congenital disease, or neurological impairment. Of the 19 subjects with children, 63 children and 12 grandchildren were examined; 26 parents, 57 siblings, and 123 second degree relatives including seven grandparents were also examined. Of the 16 subjects without children, 23 parents, 45 siblings, and 119 second degree relatives including 14 grandparents were examined. Family photographs were taken whenever possible. Pedigrees were drawn for all subjects (fig 1). Chromosomal studies on blood lymphocytes were carried out for seven subjects. The type and quality of food eaten or stored was inspected. Inquiries were made from veterinarians for epizootic diseases common in the area. Meteorological conditions during the season of conception of each case was also inquired after from the elders of the village.

Results

Clinical features—A single, immediately noticeable tumour was seen in all subjects at the root of the nose, between the eyes, or at one side of the root of the nose. The mass was spherical, ovoid, or irregular with lobulations. One subject had three distinct lobulations of which one had invaded the right orbit (fig 2). The size of the tumour varied from 1·5 cm × 2 cm ×1 cm to 7·5 cm × 9·5 cm × 7 cm. Hypertelorism was seen in most cases and was pronounced in cases where the tumour was placed on

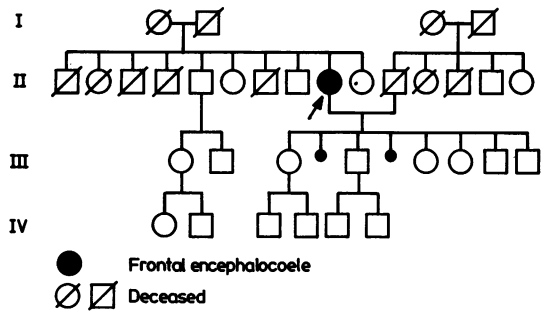

Fig 1 *Pedigree of family over four generations; woman with nine siblings, eight children, and four grandchildren. None affected.*

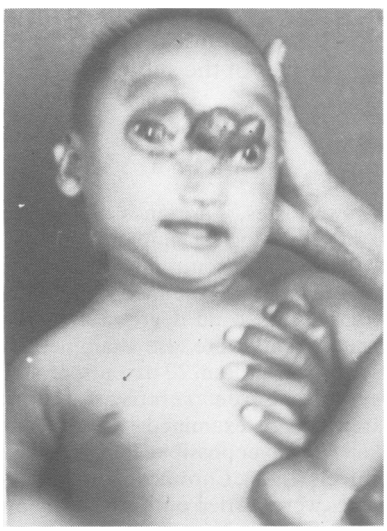

Fig 2 *Male frontoethmoidal encephalocoele with three distinct lobulations with invasion of right orbit.*

one side of the nose. The skin over the swelling was in most cases normal or shiny. Some subjects had thick, wrinkled, or pigmented skin, three had ulcers on the swelling, and one, a girl of 6 years, was leaking cerebrospinal fluid. All except two tumours were sessile. The tumour was firm, cystic, or partly cystic. Neurological examination showed no motor or sensory defects in 25 subjects; four were too young to be effectively tested. Of the others, one had anosmia, four had defective vision because of hypertelorism, and one was blind in one eye. One was mentally retarded. None had clinically detectable hydrocephalus.

Fig 3 *Female frontoethmoidal encephalocoele with her three normal children.*

Age, sex, and ethnic group—The youngest was 6 months old and oldest 59 years. Of the 19 cases with children, 12 were women and seven men. Of the 16 without children, nine were women and seven men. Among the 35 subjects, two were Karens and one Arakanese; the rest were Burmans.

Family studies—There was never more than one who was affected in a family. Only one village had two affected subjects, and they were not related. It was possible in most cases to examine family members of three generations and most of the other relatives. This was because 31 of the 35 cases lived in isolated areas and relatives could be found living in the same village or in nearby villages. Despite the isolation there was never parental consanguinity. Of individuals in the 35 pedigrees, 78% were examined (fig 3). Of the relatives not examined, 56 had died and the rest were living too far away to be contacted. None of the relatives of the index cases was found to be affected with the condition or any other congenital abnormality.

Miscarriages—Twenty six mothers of subjects reported at least one miscarriage. In 14 there was a history of two or more miscarriages immediately succeeding the index case. Of the 12 female subjects with children, six were sure of at least one miscarriage and five gave a history of two or more miscarriages. One of the latter had had five miscarriages interspersed among five normal births. Only three wives of the seven men with children reported miscarriages. All miscarriages occured between the

second and fourth month of pregnancy.

Social implications—There was no superstitious belief attached to the occurence of the condition.[11] All affected subjects were leading apparently normal lives. Their economic status was similar to other members of their community. Those who were old enough to work did not complain of any handicap in the performance of chores connected with a rural life. There was a tendency towards reclusiveness in adolescents and adults which probably helped in contacting all the cases at their respective dwellings. The attitude towards the condition was fatalistic. Only three subjects personally expressed a desire to undergo surgery for the condition when they were presented with the option. All three—two girls and one youth—were unmarried. Those who declined gave fear of neurosurgery as the main reason. Marriageability in both male and female married subjects had been determined by economic factors and not facial appearance.[7]

Environment—Thirty four subjects were paddy farmers or children of paddy farmers. One was a child of a bus driver who lived in a farming village. All mothers had eaten rice as a staple diet. Twelve mothers had taken indigenous medicine during early pregnancy. Thirty three families reared chickens, ducks, pigs, or cattle beneath their houses or in the environs. The types and incidence of epizootic diseases in villages that had cases of frontal encephalocoele were not greatly different from villages with no cases. In the villages with cases there was no evidence of undue environmental pollution compared with the general rural environment. All the subjects had been conceived and born in the villages where they lived. Flooding of the area by swollen rivers was reported to have occurred in the season of conception of 28 subjects.

Discussion

It was not possible to take *x* ray pictures of the progeny, parents, and siblings of cases of frontal encephalocoele. Impalpable osseus defects could be present in the skulls of individuals with micromanifestations of the disease. The presence of normal karyotypes in all seven cases whose chromosomes were examined was not surprising. Chromosomal disorders usually present themselves as syndromes rather than as single lesions in otherwise normal people.[12] Association with hydrocephalus was reported in several cases in a previous study of the condition but it was not observed in the present study. Banow and Simpson used ventriculograms to determine the presence and severity of hydrocephalus.[13] More elaborate methods are available now, and a proper clinical study in a neurosurgical department would render more precise results.

The miscarriage rate among mothers with frontal encephalocoele is definitely in excess of the 10·2% rate recorded in hospitals. Spontaneous abortion of affected fetuses could be a possibility, but the data obtained by personal interview indicates that a social factor is more probable. De Klerk proposed several theories on the development of the condition, all of which would lead to the presumption that the condition would be evident at birth or shortly after birth.[8] If the condition was inherited by any of the different types of Mendelian inheritance an extensive family study such as this would have shown cases in the pedigrees besides the probands. Flatz and Sukthomya found that four of 13 independent subjects had a close relative with frontal encephalocoele.[7] They also found that in two of 14 families, the parents were first cousins. In the second part of our study we reported only four subjects who had relatives suffering from the same condition. The information was obtained from patients at a neurosurgical outpatients department and a neurosurgical ward. The relatives were not seen or examined by medical personnel. During the tour of the areas made in this study, we found three subjects who had previously been reported by village headmen to be suffering from frontal encephalocoele to be actually suffering from a sebaceous cyst, a lipoma, and neurofibromas respectively. Our previous studies of the conditions in Burma reported above which included more cases have dealt with incidence, age distribution, sex ratio, geographical distribution, and other epidemiological data. The discovery of erroneous reporting of cases by non-medical personnel would indicate that previous figures, especially on incidence, should be reassessed.

A relation to flooding was seen in a previous study but ignored because it was reasonable to expect flooding during the monsoons which was the season of conception of a considerable number of cases. This study delved more deeply into the topic by intimate discussion with people in the villages. It was learnt that flooding causes a period of isolation, soaking of stored food, moulding of grain, and eating of mouldy rice. A possible hypothesis could be as follows—during a brief critical period of pregnancy, rice or a similar cereal containing a teratogen produced as an antifungal reaction is ingested. The teratogen acts on the embryo thus preventing mesodermal ingrowth which normally causes separation of the anterior end of the neural tube from the somatic ectoderm. Interposing bone is thus not formed. Neuroectoderm destined to form the brain remains attached to the skin of the frontal nasal process. Subsequent development of the face

together with enlargement of the forebrain causes intracranial structures to herniate through the osseus defect resulting in frontal encephalocoele. The fungus responsible is probably peculiar to certain geographical areas. Particular ethnic groups inhabiting these areas might possess a genetic predisposition to the condition. Sir Cyril Clarke has advised us that retropharyngeal carcinoma in chickens was found to be associated with carcinoma of the oesophagus in man in China. Congenital veterinary diseases and epizootics in the area were inquired after on the presumption that the teratogen responsible for frontal encephalocoele in man could produce observable pathological effects in domestic animals sharing the same food and enviroment. Wallace, Knights, and Dye found exencephalous young at 16 days' gestation during the necropsy of female albino mice in the eleventh generation of a DDT-treated strain.[14] The stock was maintained by matings between siblings of the affected young. Wallace, Knights, and Anderson found that the condition was inherited.[15] In affected offspring the bony vault of the skull failed to develop and the tissues of the brain were exposed. They claimed that the condition was due to a single recessive gene with full viability until birth. Giroud *et al* observed frontal encephalocoele in the fetuses of rabbits treated with thalidomide.[16] The above researchers have found specific mutagenic agents that produce developmental defects at the anterior end of the neural tube in laboratory animals. Animal responses to teratogenic agents in the environment may not necessarily imitate those of man. Epidemiologically, frontal encephalocoele could be a unique entity without any association with the other neural tube defects.

Conclusion

Children and grandchildren of people with frontal encephalocoele are not affected with the disease. Nor was any one of the parents, grandparents, and other close relatives seen in this study found to be affected. The aetiological agent is suspected to be a teratogenic substance present in fungus infected rice or another cereal.

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