THE ETIOLOGIC PATTERNS IN MICROCEPHALY WITH MENTAL RETARDATION

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Microcephaly with mental retardation forms a distinct subgroup among mentally retarded individuals. The paucity of studies on the etiology of this condition in India made the investigators to study this population. It was aimed to study the demographic and clinical characteristics, and the etiologic pattern in children with microcephaly and mental retardation. The sample consisted of 82 children who were examined by detailed clinical assessment and a battery of investigations. A definite etiology could be found in 56% of children which have been grouped into prenatal embryonic, prenatal maternal/environmental, and, birth and neonatal causes. Non-genetic causes were the most common. The prenatal etiology constituted nearly twice that of birth and neonatal causes. Majority of the etiologic factors were preventable. The role of socio-environmental factors has been discussed. As a group, the neurological disorders were found to be the most commonly associated medical condition. Malnutrition, specially of severe degree, was significantly associated with this group compared to the general population. The study findings indicate that there is a significant place for prevention.

Key words: microcephaly, etiology, mental retardation.

INTRODUCTION

Throughout human history, the relationship between the size of one's head and the level of intelligence has been the cause of much curiosity and concern. It was commonly believed that microcephaly is a certain sign of mental retardation. Several studies brought about an association between microcephaly and mental retardation (Book et al, 1953; O'Connell et al, 1965; Pryor & Thelander, 1968; Ross & Frias, 1977). However, later studies could not sustain such one to one relationship (Wood et al, 1967; Martin, 1970; Nelson & Deutschberger, 1979; Sells, 1977; Smith, 1981; Burton, 1981; Ramirez et al, 1983; Rossi et al, 1987). However, it can be inferred that decreased head size is often but not always associated with lowered intelligence and the presence of subgroups of microcephalics who typically have normal intelligence (Rossi et al, 1987) is sufficient to rule out a causal relationship between head size and intellect.

Microcephaly may be the end result of a host of etiologic agents which affect brain development during the vulnerable periods of brain growth. The abnormalities in nearly all chromosomes have been implicated in the causation of microcephaly with mental retardation. The gene for microcephaly has been traced to be located in chromosome 1 p 36 (Bloom, 1989). Among infectious agents, congenital infections with toxoplasma, rubella, cytomegalovirus (CMV) and herpes simplex virus Type 2 (HSV-2) rank prominently. Various other infectious agents like varicella-zoster (Webster & Smith, 1977), group B coxsackie virus (Johnson, 1972), congenital infections with T. pallidum (Scotti et al, 1969; Hardy et al, 1970 cited in Warkany et al, 1981), human immunodeficiency virus (HIV) (Belman et al, 1986) and meningitides due to various microorganisms (Haslam, 1987), have also been implicated in the etiology of microcephaly with mental retardation.

The inborn errors of metabolism (IEMs) that are often found include phenylketonuria (PKU), methylmalonic aciduria and hyperlysinemia. A systematic study of a large sample found IEMs in 2.1% of general population and the highest prevalence in Bangalore (Rao et al, 1980; Rao & Chandrakala, 1991). The drugs/chemicals like alcohol, diphenylhydantoin, primidone, methylmercury, carbon monoxide and isotretinoin, (reviewed in Jones, 1988) and physical agents like irradiation (Wood et al, 1967) and hyperthermia (Edwards, 1967; Pleet et al, 1981) have been implicated.

Even though severe and long standing malnutrition has been implicated in the etiology, recent literature indicates the controversial nature of this association (Frisch, 1972; Dobbing, 1985). Several other maternal factors like maternal diabetes, PKU, uremia, hypoglycemia, eclampsia and placental deprivation of supply have also been shown to be of etiologic significance.

Many causes are sporadic and no underlying cause is identifiable in some cases, like in some well known syndromes like Rubinstein-Taybi syndrome,

Langer-Gideon syndrome etc. The head size may be normal at birth and later may not grow to adult size, when the disease process occurs beyond the neonatal period, as in the "walnut brain syndrome" (Laurence & Cavanaugh, 1968).

Thus, microcephaly reflects a pathologic change in brain structure with an effect upon intelligence dependent upon the extent and type of underlying pathology (Cowie, 1987). The presence of mental retardation in a person with microcephaly indicates sufficiently severe neuropathological changes, forming a distinct subgroup among those with mental retardation from the point of view of understanding the etiopathogenesis. Very few studies have been done in India (Narayanan, 1981) and no studies on the etiology of this group are available.

AIMS OF THE STUDY

1. To delineate the demographic and clinical characteristics such as degree of mental retardation, associated medical and psychiatric problems, other additional handicaps such as specific speech delay and nutritional status associated with microcephaly, and

2. To study the etiologic pattern of microcephaly with mental retardation.

MATERIALS AND METHODS

The sample consisted of eighty two successive subjects attending the Mental Retardation Clinic of NIMHANS, who satisfied the following inclusion criteria:

1. Head circumference (HC) greater than 3 SD below the mean for age and sex, as per the head circumference chart (Roche et al, 1987).

2. Mental retardation as defined in DSM III R (American Psychiatric Association, 1987).

3. Informed consent from the parents.

4. Age was fixed at eighteen years for both sexes initially. After the assessment of a few cases above 3 years of age, it was observed that the reliability of information in some cases was questionable. Consequently, the cut-off age was reduced to three years for both sexes.

A composite proforma was developed incorporating the items from the National Institute for Mentally Handicapped - National Institute of Mental Health and Neurosciences (NIMH-NIMHANS) Mental Retardation Case Record to collect relevant details from parents and other reliable informants.

The place of residence, socioeconomic status, and the type of household were assessed based on the criteria given in the Case Record. A minimum of three generations were studied using the pedigree chart, to collect the family history. The psychosocial inadequacies were assessed according to Rutter's axis V listing of psychosocial inadequacies (Rutter et al, 1975), accepted in the ICD-9 (World Health Organization, 1978) multiaxial system of diagnosis for children and adolescents. A section on the physical examination, which included the congenital anomalies that commonly occur with syndromes in which microcephaly and mental retardation are seen, was developed and incorporated into the proforma.

Current psychiatric disturbances were assessed using a specified format. The maladaptive behavior scale was administered to each child. This composite proforma was administered to five children to check whether adequate information can be collected. These children were not included for the study. The actual study started only after observing that the proforma collects adequate information.

The maximum occipito-frontal measurement taken by a non- stretchable tape was considered to be the head circumference. Mental retardation was assessed clinically and by psychometry. Wherever verbal and comprehensive abilities were adequately developed, Binet-Kamat Test was administered and for other children Vineland Social Maturity Scale was used.

The nutritional status was assessed using the Gomez type chart. The malnutrition severities were graded as per the recommendations of the nutrition subcommittee of the Indian Academy of Pediatrics (cited in Park & Park, 1983). A section for interpreting the investigation results has also been included. Each child was diagnosed along NIMHANS multi-axial diagnosis for persons with mental retardation which is a modification of Rutter's (1975) multiaxial system of diagnosis for children and adolescents, viz,

Axis I: Degree of mental retardation

Axis II: Possible etiology or syndromal diagnosis

Axis III: Associated medical disorder

Axis IV: Associated psychiatric illness

Axis V: Parental knowledge, expectations and adverse psychosocial situations.

The following investigations were done to detect the etiologic factors and/or associated medical disorders:

1. Complete hemogram

2. Urinalysis: The urine was collected in three different sample bottles and analyzed on the same day:

- for the presence of glucose and albumin, and microscopy for evidence of bacteria, pus cells, casts etc. .

- for abnormal metabolites in urine (for the presence of PKU, homocystinuria, mucopolysaccharidosis, and aminoacidurias).

- for metachromatic granules.

3. Karyotyping was done based on the method of Arakaki and Sparkes (1963, cited by Manjunatha & Rao, 1990).

4. Enzyme linked immunosorbent assay (ELISA) for the detection of IgM antibodies against CMV, Rubella, HSV-2, Japanese encephalitis virus (JEV), HIV, Toxoplasma gondii on serum samples. VDRL slide flocculation test was carried out on these samples to rule out congenital syphilis.

5. Radiologic assessment: X-Ray Skull- Lateral view was done for all children. CT scan brain was done in selected children.

Five ml of blood for hemogram and serologic tests were collected in two separate bottles, under strict aseptic precautions. The lumbar puncture was done on the same day under similar conditions. Three ml of CSF was collected. Hemogram was done on the same day whereas another sample of serum and CSF were coded and stored at -70°C, and analyzed at the end of data collection period blind to clinical details. After the titres were obtained, the codes were deciphered and the test results ascribed to appropriate cases. For karyotyping, the blood was collected in heparinized syringes and was injected into the medium on the same day. All positive and doubtfully positive samples were retested for confirmation. Only when the samples turned out to be positive in at least two of the three samples were they considered definitely positive.

RESULTS

SOCIODEMOGRAPHIC DATA

About 70% of the sample consisted of children under 3 years of age (Table 1; the mean age, 2.42± 3.1 years, the median, 1.67 years, and the mode, 11

Table 1
Frequency distribution of the sample according to age and sex

Age/Sex	Male	Female	Total	Percent
0-12 months	11	14	25	30.25
13-24 months	15	8	23	28.05
25-36 months	4	5	9	10.96
37-48 months	5	3	8	9.76
49-60 months	5	0	5	6.10
61-72 months	3	0	3	3.66
72 months	6	3	9	10.96
Total	49(59.8%)	33(40.2%)	82	100%

months). Nearly 60% of the population comprised males which is in contrast to the findings of Opitz et al, (1978, cited in Warkany et al, 1981) and Prasad et al (in press) where a higher prevalence in females have been reported (Table 1). A significant proportion of children were from socio- economic levels IV and V (X^2 19.12 , df=2, p<0.001) and were living in slums, rural or semiurban areas. The illiteracy among parents was 28% and the maternal illiteracy was 40%. Nearly 70% of fathers were either semi-skilled or skilled workers.

FAMILY BACKGROUND AND HISTORY

Consanguinity was present in 45% of parents. A positive history of mental illness was present in 9.75% of fathers and 4.87% of mothers. In addition, a family history of mental retardation and other mental illnesses was present in 19.5% of families each, and microcephaly and epilepsy in 7.3% of families each. It was found that nearly 81% of families had at least one distortion or inadequacy in the psychosocial environment of the family, significant enough to be coded on axis V. A majority of children were living in conditions of inadequate social, linguistic and/or cognitive stimulation (76.5%). About 23% of children were living in inadequate living conditions. Nineteen percent of the families had none, 37.8% had one, 31.7% had two and about 11% had three or more significant distortions/inadequacies in the psychosocial environment.

ETIOLOGIC FACTORS

Table 2 shows the frequency distribution of children who underwent different assessments and investigations. The etiologic factors were divided into prenatal, birth and neonatal, and postnatal factors. Prenatal etiologic factors was present in about 16% and birth and neonatal factors in 17% of children (Table 3). However, no definite postnatal

Table 2
Frequency distribution of children who underwent different assessments and investigations

Assessment/ Investigations	Male	Female	Total	Percent
Clinical assessment	49	33	82	100.00
Psychometry	49	33	82	100.00
Complete hemogram	24	20	44	53.65
Urine analysis:				
- Routine	49	33	82	100.00
- Abnormal metabolites	49	33	82	100.00
- Metachromatic granules	45	24	69	84.14
X-Ray Skull (lateral view)	46	29	75	91.46
Serological studies	48	27	75	91.46
Cytogenetics	29	13	42	51.22

Table 3
Distribution of etiologic factors in the sample

Factor	Male	Female	Total	Percent
Prenatal				
1. Attempted abortion	1	1	2	2.44
2. Threatened abortion	1	1	2	2.44
3. Antepartum hemorrhage	0	1	1	1.22
4. Rh incompatibility	2	0	2	2.44
5. Eclampsia	1	0	1	1.22
6. Irradiation	1	0	1	1.22
7. Infections	3	1	4	4.88
Birth and neonatal				
1. Precipitate labor	1	1	2	2.44
2. Prolapsed cord/ Cord round the neck	2	0	2	2.44
3. Infections	3	3	6	7.32
4. Delayed birth cry*	24	13	37	45.12
5. Respiratory distress*	8	1	9	10.98
6. Feeding problems*	15	9	24	29.27
7. Convulsions*	16	5	21	25.61

Table 4
Etiologic pattern of microcephaly and retardation

Etiology	Number	Percent
Prenatal		
Embryonic	11	13.40
Chromosomal	1	1.22
Single gene disorder	4	4.88
Other specific disorders of presumed genetic origin	4	4.88
Others	2	2.44
Maternal/Environmental	15	18.3
Total	26	31.7
Birth and neonatal		
Labor related	4	4.88
Neonatal encephalopathy	10	12.20
HIE	4	4.88
Septicemia	6	7.32
Total	14	17.08
Prenatal and birth and neonatal	6	7.32
Unknown	36	45.90

etiologic factors could be found. There was no significant association between these groups of etiologic factors and the severities of mental retardation and microcephaly.

Mere presence of etiologic factor was not considered to be the evidence of etiology, unless the known effects of the factor in question was observed in a given child. When a combination of at least one definite prenatal factor, microcephaly detected at birth and at least five congenital anomalies were present, the child was considered as having a definite prenatal etiology. Ten perinatal factors were considered as having etiologic role. In addition, three factors marked with an asterisk in table 3, were used to assess hypoxic-ischemic encephalopathy (HIE) in the new born. The presence of these factors together was taken as indicative of HIE, which was present in four children. These groups of etiologic factors were considered individually and in different combinations.

Table 4 shows the analysis of etiology. Thus, in about 56% of children definite etiology could be established. Four (16% of those below one year of age) infants were positive by ELISA for IgM antibodies for various infections, which means that the infections have occurred during the prenatal period. There was evidence of infection with rubella in one, CMV in two and HSV-2 in one, infants.

X-Ray skull (lateral view), which was done on 75 children, did not show any significant abnormality. CT scan (brain) could be done on only four children. One child showed absence of corpus callosum, who was also positive for CMV by ELISA.The child could not fit into any of the known syndromes where absence of corpus callosum is a feature. The second child showed massive infarction of cerebral hemispheres which had possibly occurred prenatally, probably due to impaired development of carotid system of vessels. The third child showed calcification of basal ganglia structures with cortical atrophy, predominantly in the frontal lobe. Clinically, the child showed only hypotonia. This child had normal developmental milestones up to 6-9 months of age and later deteriorated fully. The fourth child showed aqueductal stenosis with hydrocephalus. None of these three children showed any evidence of prenatal infections.

Four (4.88% of the sample) children with autosomal recessive microcephaly were detected. The association of the latter with family history of microcephaly was found to be highly significant (Fisher's exact probability test, p = 0.0009). However, the association with consanguinity and family history of mental retardation was not significant.

In forty two children, karyotyping was done and no abnormality could be detected. One child, on Q banding showed several breaks in the chromosomes. The karyotypes of parents were normal. As the child was a partial albino, the significance of this finding is questionable. This child had normal attainment of milestones till about five months of age and then started deteriorating. Both the parents had Hansen's disease (multibacillary variety) and were declared cured after multidrug treatment three years before the conception. The mother's age at conception was thirty nine years.

ASSOCIATED MEDICAL AND PSYCHIATRIC CONDITIONS

Among the associated medical conditions, malnutrition, anemia and neurological disorders were the most prevalent medical conditions (Table 5). About 23% of children had associated psychiatric disorders. Although 11% of children had autistic features, only two could be diagnosed as atypical autism according to ICD-10 (World Health Organization, 1992).

About 63% of children assessed for nutritional status, were malnourished, which is significant compared to the prevalence in the general population (X^2

Table 5
Associated medical and psychiatric disorders

Condition	Frequency of occurrence	Percent
Medical		
Malnutrition	50	60.97
Anemia: total	39	51.31
Iron Deficiency	32	-
Dimorphic	6	-
Not subtyped	1	-
Neurological		
(Seizures, cerebral		
palsy and others)	72	87.80
Sensory handicap	3	3.66
Others	25	30.47
Psychiatric		
ADHD	6	7.32
Autistic features	9	10.88
BD NOS	3	3.66
Conduct disorder	1	1.22

13.33, p<0.001). The prevalence of severe degree of malnutrition in this sample also was highly significant (X^2 42.5, p<0.001) compared to the general population. In addition, no significant relationship could be found between the severity of malnutrition and the severity of mental retardation and microcephaly.

OTHER FINDINGS

The congenital microcephaly was detected in 46.34% (n=38) of the sample. This was based on hospital records and parental observation. About 21% of children in this group had etiology attributable to prenatal embryonic factors. There was no significant association with consanguinity, family history of mental retardation or microcephaly. Out of them, four had autosomal recessive microcephaly. In addition, there was no significant relationship between the severities of mental retardation and that of microcephaly.

The hemogram revealed reactive lymphocytes and lymphocytosis in 49.32% and 36.98%, respectively. In addition, eosinophilia was seen in 67.12% and vacuolated lymphocytes in 13.7%.

DISCUSSION

STUDY DESIGN AND METHODOLOGY

The purpose of this study was to examine various factors like maternal, environmental, genetic and others which have a bearing on the causation of microcephaly and mental retardation. The assessment proforma was so structured to focus more on identifying the etiologic and other possible con-
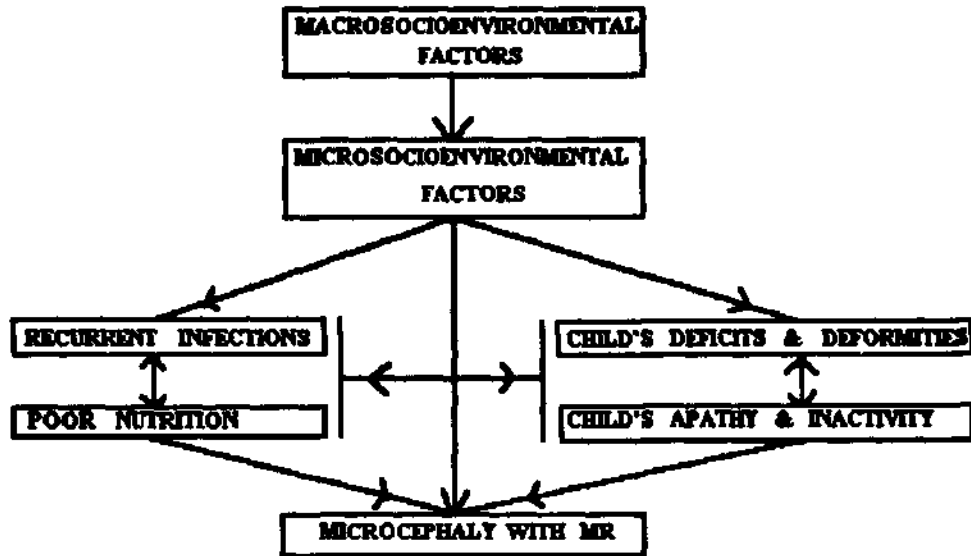
FIG 1: SOCIOENVIRONMENTAL RISK HYPOTHESIS

Macrosocioenvironmental Factors: Maternal age <18yrs but >30yrs = 25%; Maternal Illiteracy= 40%; LSES =94% Unskilled/Semiskilled Occupation = 70%.

Microsocioenvironmental Factors: Psychosocial Inadequacies = 80%.

Poor Nutrition: Significantly high compared to general population.

tributing factors. The near total dependence on the recall of events by parents regarding pre-, peri- and postnatal periods, and childhood was partially overcome by collecting the information from the relatives and wherever available, hospital records too.

It was decided that the head circumference chart should: 1) give the head circumference from birth to 18 years, 2) be available for every month in the first year, as the head circumference increases rapidly during this period, 3) give standard deviation for each measurement and there should not be wide fluctuations in them, 4) be applicable to the Indian context, and 5) be cross validated across different races and countries. The chart used in this study meets all the criteria except [2].

The measurements for every month in the first year are not available; instead, figures for the first, the third, the sixth and the ninth month are available in the same chart. The head circumference measurements in this chart compare well with those given in ICMR manual on growth and development of Indian infants and children (ICMR, 1989), but for standard deviations which have wide fluctuations in the latter. In addition, the head circumference measurements

in this chart have been cross-validated with the composite international and interracial graph of Nellhaus (1968).

The laboratory techniques that have been used are reliable. The validation of these tests were done as per the recommendations of the manufacturers.

Head circumference was measured only once during the assessment and the presence or absence of microcephaly, decided cross-sectionally. Several investigators have recommended serial head circumference measurements (Avery et al, 1972; Dolk, 1991), as a single measurement below the cut-off limit does not reveal the actual status of growth and development of the brain. This could not be done because, the follow up assessments were not included in the study design.

SOCIOENVIRONMENTAL RISK HYPOTHESIS

The socioenvironmental factors are divided into micro-socioenvironmental and macro-socioenvironmental factors. The maternal age and literacy, socioeconomic strata, occupation of the father etc., constitute the latter while the inadequacies in the

immediate environment in which the child is brought up constitute the former. The interplay between these two groups of factors in children with microcephaly and mental retardation can be postulated. The lower socioeconomic strata, illiteracy - specially of mothers, determine the microenvironmental factors such as the quality of care during prenatal, perinatal and postnatal periods, nutrition, sanitation etc., in which the child develops. These, in turn, predispose the children to recurrent infections and malnutrition. The child's own apathy or inactivity due to these factors and/or due to the deficits resulting from microcephaly with mental retardation, and, perhaps the deformity in more severe forms, may lead to neglect and under-stimulation of these children. The latter worsens the apathy of the child. Consequently, the child is almost inescapably caught in a vicious circle (Fig 1). The long term follow up studies of Stoch and Smythe (1963 & 1968) support these findings.

Even though primary etiologic role cannot be ascribed to these factors, a major contributory role cannot be denied. These factors may even perpetuate the effect of biological and physical agents. This assumes great significance in view of the fact that many of these psychosocial factors are largely preventable, which seems to be widely prevalent in India. Figure 1 shows the magnitude of the problem as found in this study. As the sample is not truly representative of the general population, cautious extrapolation needs to be made. A study of these children in general population would yield more definitive conclusions.

THE ANALYSIS OF ETIOLOGY

The criteria to detect prenatal etiology which includes the presence of a definite prenatal factor, microcephaly at birth and five or more definite congenital anomalies is quite valid. The latter two criteria have been included to reflect the influence of the prenatal etiologic factor on the growing embryo/fetus. For the purposes of discussion, the prenatal etiology may be grouped as follows: 1) prenatal embryonic, and 2) prenatal maternal/ environmental etiologies.

The prenatal embryonic etiology could be discerned in 13.4% of cases (n=11; Table 4). Single gene disorder in the form of autosomal recessive microcephaly was found in four children. The significant association with family history of microcephaly in this small group reflects the importance of genetic factors (Fisher's exact probability test, p=0.0009). Four children could be grouped under other specific syndromes of presumed genetic origin. One child with Rubinstein-Taybi syndrome and one with Angelman syndrome were included in this subgroup. The third child had hydrocephalus secondary to aqueductal stenosis. The fourth child revealed absence of corpus callosum on CT scan. In addition, this group also consisted of children with unknown prenatal embryonic etiologies. Two children had uneventful pre, peri and postnatal periods; had normally attained milestones up to about six months of age, following which they deteriorated in terms of their milestones. One of these children had several breaks in her chromosomes seen on banding; the other child had calcification of the basal ganglia and atrophy of the cortex, predominantly in the frontal lobes, with gross hypotonia on clinical examination. The third child had infarction of cerebral hemispheres, which had possibly occurred prenatally. Even though G banding was done on the samples, high resolution banding (HRB) could not be done on any of them which would have certainly yielded much more information than what is available now. It can be presumed here that most of the above cases would have genetic etiology.

One study conducted in India on children with mental retardation revealed chromosomal abnormality in 15.5% and chromosomal variants in 4% (Reddy & Thomas, 1985). Several surveys conducted across the world have revealed chromosomal etiology varying from 5% to 21% (reviewed by Reddy & Thomas, 1985). However, the authors could not find any such survey done on children having microcephaly and mental retardation together.

Prenatal maternal/environmental etiology could be discerned in 18.3% of children (n=15; Table 4). The infections were evident in 16% of infants which can be considered to be etiologically significant. The congenital CMV infection in the general population in the US is 1% of newborns (Hirsch, 1991) and 4% among children up to 5 years in London (Stern & Elek, 1965). Even though the prevalence of CMV infections among infants in India is not definitely known, several studies have shown a considerably high figures for children which is fairly consistent across various reports and ranges from 66.7% in Pondicherry (Madhavan et al, 1974) to 83% in Chandigarh (Pal et al, 1972). In this sample it was found to be 8% of infants.

Four percent of infants in this sample had serological evidence for infection with HSV-2 infection. In the US, the incidence of neonatal HSV infection is 13.8/100,000 live births (McKendall, 1989). In one of the studies from India prevalence of HSV-2 infection was found to be significantly high (p<0.01) among children below 10 years of age hailing from rural areas compared to those from urban areas (Seth et al, 1981). One infant (4%) was positive in the serum for IgM against JEV. The available world literature does not indicate whether JEV infection can cause microcephaly with mental retardation. Only one child was exposed to irradiation, when X-ray KUB region was taken for the mother. Even though the exact dose was not known, this was considered as a definite etiologic factor. The rest of the factors included in this subgroup are also potentially preventable. The concerning issue is that there is relative predominance (58%) of non-genetic causes among prenatal etiologies which are largely preventable.

Birth and neonatal etiologies have been divided into those related to labor and neonatal encephalopathy. In this sample, neonatal sepsis was found in 43% in those coming under this category (7.32% of the total sample). HIE was found in about 5% of the sample. Severe neonatal sepsis is known to cause impaired cerebrovascular autoregulation leading to systemic hypotension (Hill & Volpe, 1989) which in turn leads to impaired balance between demand and supply in the vulnerable periods of growth and differentiation of the brain. The prolapsed cord and the precipitate labor accounted for the rest of the etiologies in this group. The etiologic significance of these factors has been established in various other studies.

A combination of prenatal and perinatal factors were present in 7.3% of the sample. Table 4 shows the pattern of etiology in this study.

A point worth noticing in this study is that the majority of (about 75%) of these etiologies, except for genetic causes, are potentially preventable. The vicious circle formed by the alarming magnitude of the various socioenvironmental risk factors in which the children are caught is another finding of pragmatic value. These are the unique findings of the present study and are of seminal importance to the current national health and social scenario in India. This also reflects, perhaps, poor percolation of the maternal and child health (MCH) services to the masses at large. The authors are of the opinion that earnest implementation of the existing national program of MCH services with a few modifications like screening of all children for TORCH infections and for STD would go a long way in reducing the incidence and morbidity arising out of this condition.

ASSOCIATED MEDICAL AND PSYCHIATRIC CONDITIONS

Considering the method of assessment of the nutritional status, the significant association of malnutrition in general, and severe degrees of malnutrition, in particular, could be explained in several ways, viz., a biologically determined short stature and small build, the presence of feeding problems and inappropriate feeding practices, the recurrent infections consequent to inadequate nutrition and other micro- and macro-socioenvironmental factors could have contributed to the greater frequency of occurrence. The fact that the severity of malnutrition was not significantly associated with severity of either microcephaly or mental retardation, shows that the primary etiologic role of malnutrition is quite minimal/absent.

Malnutrition as an etiologic factor is controversial. The findings of animal studies have not been adequately corroborated to human beings. The reduction in brain weight, myelin and DNA have been demonstrated by several workers. There is also evidence for the recovery of animals after a period of undernutrition (DeLevie & Nogrady, 1970). The malnutrition during cell replication has been shown to produce permanent defects in humans (Fish & Winick, 1969; Hoorweg & Stanfield, 1976). Based on these facts, it can be postulated that chronic and severe malnutrition is a very important micro-socioenvironmental factor in the etiology, rather than a primary etiologic factor.

As a group, the neurologic disorders (seizures, cerebral palsy, monoparesis etc,) were the most common associated medical conditions. This reflects the prevalence of underlying structural abnormalities of brain. Perhaps this can also explain the predominance of severer forms of microcephaly and mental retardation in this sample.

The presence of eosinophilia and reactive lymphocytosis, on hemogram, in a considerable proportion of the sample could be due to chronic ongoing viral or parasitic infection, or some sort of immunodeficiency or both. This can be argued as either the cause or the consequence of recurrent infections. The role of recurrent infections in perpetuating the deficits has been discussed earlier (see Fig 1 and the section on "socioenvironmental risk hypothesis").

However, this needs to be tested by comparing these figures with non-microcephalic mental retardation children and normal children as controls.

The relatively lower prevalence of psychiatric disturbances in this sample (taking the range as between 30% and 60% of retarded individuals) may be because of the predominance of younger population in this sample.

OTHER FINDINGS

The severities of microcephaly and mental retardation were not significantly associated with each other. This is in keeping with the present view that it is the extent of underlying pathology in the brain that determines the degree of retardation not just the head size (Cowie, 1987). The more severe forms of microcephaly and mental retardation, and greater prevalence of neurological disorders in the sample is reflective of children with severer forms of underlying pathology in their brains.

In conclusion, it can be stated that a large proportion of children with this condition can potentially be given the advantage of early detection of etiology with these simple investigations and appropriate management. This study also brings out the predominance of preventable etiologies in India. In addition, the role of various socioenvironmental factors in perpetuating the pathologic process in this subgroup has been postulated. Further broadening of the investigational base has been suggested. It can be inferred that the prevention at primary, secondary and tertiary levels are of utmost importance in this subgroup.

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