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Aetiology of mild mental retardation

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SUMMARY A clinical and family study was carried out in 169 children attending schools for the mildly mentally retarded in Southampton to assess the prevalence of recognised medical risk factors; 71 children (42%) had such risk factors. These were prenatal in 22, perinatal in 41, and postnatal in eight. Risk factors of possible, but less certain, significance were found in a further 63 children (37%). In 86 families (51%) there was a history of serious educational problems in both parents. The prevalence of both types of risk factor was higher in the children whose parents had no educational problems. There were, however, 25 children (15%) whose parents had no history of educational problems and in whom medical risk factors were either absent or minimal.

The traditional view that mild mental retardation is largely caused by polygenic and sociocultural influences has been challenged by recent studies.[1–3] Increasing ability to identify genetic syndromes, chromosome abnormalities, and biochemical defects associated with mental retardation, has extended the scope of diagnosis and the possibility of attributing mental retardation to a specific cause. We therefore undertook a study of children attending schools for the mildly mentally retarded to assess the contribution of medical, and especially genetic, factors of recognised aetiological importance. Medical factors of possible but not fully established relevance were also recorded. We hoped to assess the extent to which mild mental retardation in the local population might be reduced by early diagnosis followed by treatment, genetic counselling, or prenatal diagnosis.

Children identified as having delayed development during preschool years are usually seen by a paediatrician for assessment, but mild mental retardation may not be apparent until after a period in a normal school. Children referred for special education at this stage are not usually referred for a paediatric opinion unless there is a specific indication. We hoped that this study would provide guidelines for the medical investigation of children attending schools for the mildly mentally retarded. Non-medical factors such as parental education and home environment are considered briefly here, but are the subject of another report.[4]

Patients and methods

Schools for the mildly mentally retarded provide education for children with learning difficulties; there are separate schools for children with physical handicaps. Southampton is well provided with facilities for mildly mentally retarded children. Referral requires parental approval but is otherwise unrestricted. The survey was carried out before the 1983 Education Act which encourages integration of 'less able' pupils into normal schools, and hence children were more readily referred than at present.

The study population was drawn from children aged 7–11 years attending the three Southampton schools that provide education for mildly mentally retarded children. At the time of the study the total school population aged 7–11 years was 11 921, of whom 229 (2%) attended schools for the mildly mentally retarded. One hundred and sixty nine children (93 boys and 79 girls) were included in the study. The parents of 31 children declined to take part and the parents of 19 did not actively refuse, but did not cooperate. Six children who were in foster homes and four who left school in the course of the study were also excluded.

Children referred to schools for the mildly mentally retarded do not always have their intelligence quotient (IQ) tested beforehand. Referral is usually because of an inability to cope with normal education, and IQ assessment by an educational psychologist is secondary. Eighty nine (53%) children in the survey had IQs within the accepted range of mild mental retardation (IQ 50–70).[5] Seventy five (44%) were of borderline intelligence (IQ 71–85). Five (3%) had not had a formal test. The study was therefore not confined to children with mild mental retardation, but included children of borderline intelligence whose learning problems had been sufficient to merit referral to a special school.

With the cooperation of head teachers and with the knowledge of family doctors, parents of children attending the schools were invited by letter to take part in the survey. Those who agreed were visited at home where a family history was taken and parents were asked about their own medical and educational backgrounds. They were asked for details of pregnancies, and the births, early development, and education of all their children. Blood and urine specimens were taken from the mothers, and written permission was obtained for study children to be seen and tested. School medical records and hospital records were checked for information about the children's medical histories.

At school each study child had a detailed clinical examination that included measurements of height, weight, and cranial circumference, and inspection for minor malformations including abnormal skull shape, unusual facies, abnormal ears, hypertelorism, epicanthic folds, high palate, asymmetric chest, wide spaced nipples, clinodactyly, single palmar crease, abnormal finger creases, minor malformations of fingers and toes, and abnormal dermatoglyphics. Coordination was tested by hand tapping, finger/thumb and finger/nose apposition, heel/toe walking, and hopping. The child's performance in each test was rated as satisfactory or poor.

Table 1 *Medical features of probable aetiological importance in 71 mildly mentally retarded children*

Aetiological feature	*No of children*
Prenatal:	
Chromosome abnormality	8
Malformation of the central nervous system	5
Infection	2
Sotos' syndrome	1
Aarskog's syndrome	1
Rubenstein-Taybi syndrome	1
Cohen's syndrome	1
Prader-Willi syndrome	1
Alcohol fetopathy	1
Inborn error of metabolism	1
Perinatal:	
Twitching or cyanosis during first week	16*
Apgar score <7 at 5 minutes	16†
Fetal distress	10‡
Blue or limp at birth	4
Postnatal:	
Infection of the central nervous sytem	3
Apnoea	2
Status epilepticus	1
Intracranial haemorrhage	1
Severe pertussis	1

*Includes two with prenatal signs; †includes three with prenatal features; ‡diagnosed by obstetrician.

Poor performance in two or more tests indicated incoordination. The same series of measurements, examination for minor malformations, and coordination tests was carried out on 55 children in the same age range attending normal schools. Blood and urine samples were taken from the study children. All urine samples were screened by standard methods for glucose, protein, blood, ketones, cysteine, cystine, and homocystine. Quantitative amino acid analysis was done on mothers' blood samples with a Rank-Hilger-Chromaspeck amino acid analyser. Blood spot screening for hypothyroidism and phenylketonuria, and chromosome analysis including examination for the fragile (X) chromosome, were done on children's blood samples.

Perinatal factors in index children with no major prenatal or postnatal factors were compared with those of their unaffected siblings (attending normal schools) who acted as paired controls. The control sibling was defined as the one nearest in age to the index patient, and those index patients with no unaffected siblings were left out of the comparison.

Postnatal events were considered significant if the child had been developing normally before the event, but showed developmental delay thereafter.

Results

KNOWN RISK FACTORS

Medical features that probably contributed to the referral were identified in 71 of 169 children (42%). (table 1). Only five children had more than one such feature, and all of these had a combination of prenatal and perinatal features.

Prenatal features

Chromosome abnormalities were present in eight of 22 children with prenatal features. These have been described elsewhere.[6] Three children—two girls with Down's syndrome, and a boy with karyotype 46,XY,14q+—were known to have a chromosome abnormality before the survey. The others included three boys with sex chromosome aneuploidy—47,XXY (2), and 48,XXYY (1), one girl with an autosomal deletion—46,XX,del(15)(q11·2;q13·1), and one girl with an X-autosome translocation, 46,X,t(X;19). None of these five children had obvious dysmorphic features. Mothers of four children—the two with Down's syndrome, one boy with Klinefelter's syndrome, and the girl with karyotype 46,XX,del(15)—were aged 38 years or over when the children were born.

Two children had 'Mendelian' syndromes; one boy had Sotos' syndrome and his mother also had features suggestive of the syndrome. One boy had

Aarskog's syndrome. There was no family history of retardation, but his mother and grandmother were of short stature and had ptosis. Three children had 'non-Mendelian' syndromes associated with mental retardation. One boy had Rubinstein-Taybi syndrome, which had been identified at birth. Two children were identified in the survey; one girl had Cohen's syndrome, and one had Prader-Willi syndrome, without a demonstrable chromosome abnormality. Of three girls with microcephaly, one had minor dysmorphic features that did not fit into any recognised syndrome; the other two had no associated physical features. All three had pronounced incoordination. Two boys had hydrocephalus, one of which had been diagnosed and treated surgically when he was referred for a clicking hip at the age of 4 weeks. The other, born at 34 weeks' gestation, had birth asphyxia and a stormy neonatal course. Hydrocephalus, noted at 7 weeks of age, was not treated surgically.

Two children had had prenatal infections. Toxoplasmosis was diagnosed at the age of 9 months in one child who had severe retinal scarring and intracranial calcification. The mother of one boy had acquired syphilis in the first trimester, and he had antibodies present at birth. One child, with an alcoholic mother, had features of the fetal alcohol syndrome. One other mother admitted to heavy drinking in pregnancy; her child had an X-autosome translocation but no features of fetal alcohol syndrome. Congenital adrenal hyperplasia had been diagnosed in a child at the age of 5 days. This led to a crisis seven weeks later with fitting, opisthotonos, and subsequent facial palsy. The investigations carried out on urine and blood samples did not show any biochemical defects in mothers or children, nor any hypothyroidism in the children.

Perinatal features

Nineteen children had been born outside the Southampton district; birth records for nine could not be traced, but the mothers gave no history of perinatal problems. Six children had been born at home: one was admitted to hospital blue and limp shortly after birth, but there was no history of perinatal stress in the other five. Thirty nine children had been born in small peripheral hospitals where Apgar scores were not routinely recorded. Three of these children who were blue and limp at birth and were transferred to special care units have been included in the group with recognised perinatal stress. A history of perinatal stress was the only recognisable risk factor in 41 children. Five children with an adverse perinatal history also had a significant prenatal feature—two children had chromosome abnormalities (47,XXY, 46,XX,del(15)), and one boy with hydrocephalus had low Apgar scores; the other hydrocephalic boy and the child with congenital adrenal hyperplasia had recorded neonatal twitching.

Table 2 *Perinatal features in 120 mildly mentally retarded children and paired siblings receiving normal education who acted as controls*

	No of study children	*No of normal children*
No adverse feature	87	111
Adverse features:		
Fetal distress	9	3
Apgar score <7 at 5 minutes	11	5
Blue or limp at birth	2	1
Twitching or cyanosis during first week	11	0

One hundred and twenty study children with no recognisable prenatal or postnatal risk factors had siblings receiving normal schooling. The perinatal features of the study and control groups are shown in table 2. Recordings of fetal distress or low Apgar scores were less than half as common in the control as in the study group. No child in the control group had recorded neonatal twitching or cyanosis. Overall, the incidence of adverse perinatal factors was significantly less in the control group ($p<0{\cdot}001$).

Postnatal features

Two children had had meningitis, aged 6 and 9 weeks, respectively, and one girl had had encephalitis when she was 3 years old. One boy found cold and limp in his cot when 3 weeks old, and another found apparently lifeless in his pram at 6 months, were regarded as 'rescued cot deaths'. Both these children had behaviour problems. One boy, when aged 18 months developed status epilepticus which took three to four days to come under control; he also had a behaviour disorder. One child developed bilateral subdural haematomas after a non-accidental injury, and she had a residual hemiparesis. The last child in this group was developing normally until he had prolonged pertussis at the age of 2 years. He has since been physically as well as mentally delayed, with small stature and retarded bone age.

POSSIBLE RISK FACTORS

One hundred and six study children had in their history or examination medical features of possible relevance but with no established link with retardation. Forty three of these children also had recog-

nised risk factors. Of 63 children with risk factors of only possible relevance, 37 had just one feature, and 26 more than one (table 3).

Three children had been born to mothers with type I diabetes and in all three this was the only medical factor noted. Insulin control was reasonable—none of the mothers had 'brittle' diabetes. One of the children weighed 4770 g (>97th centile) at birth but there were no problems at delivery; the other two children had birth weights within normal limits. Four children—all boys—had major malformations not affecting the central nervous system; three had cleft lip and palate, one of whom also had Poland's anomaly. The fourth child had a ventricular septal defect that was successfully repaired when he was 2 years old.

Twenty one survey children were born at or before 36 weeks' gestation, but in none was this the sole feature. Thirty survey children (18%) had heights on or below the third centile. Ten of these children had no other medical feature. Four of 55 control children (7%) had this degree of short stature. Ten children (6%) had cranial circumferences on or above the 97th centile. This was the sole medical finding in four. Two control children (4%) had this degree of macrocephaly. Twenty one children (12%) had severe behaviour problems, all but two of whom had other medical features. Of the

Table 3 *Medical features with no well established link with mental retardation in 106 mildly mentally retarded children*

Feature	*No of times each feature present (n=106)*	*No of children in whom this was sole medical feature (n=37)*	*No of times this feature was accompanied by a known risk factor (n=43)*	*No of times this feature was accompanied by one or more other feature (n=26)*	
				One	*More than one*
Prenatal:					
Twinning	9	0	2	2	5
Chromosome translocation	1	0	0	0	1
Maternal diabetes	3	3	0	0	0
Maternal drug taking	6	0	2	2	2
Maternal operation	1	0	0	0	1
Maternal injury	2	1	0	1	0
Threatened abortion	8	1	4	2	1
Hyperemesis	14	2	7	3	2
Maternal toxaemia	14	4	9	0	1
Maternal anaemia	5	0	1	0	4
Small for gestational age	11	1	5	2	3
Major malformation	4	1	2	0	1
Perinatal:					
Gestation <37 weeks	21	0	11	2	8
Antepartum bleeding	4	1	0	1	2
Rapid delivery	3	1	1	0	1
Neonatal jaundice	10	0	7	0	3
Excessive weight loss	1	0	0	0	1
Postnatal:					
Severe malnutrition	2	0	1	0	1
Immunisation reaction	1	0	0	0	1
Head injury	2	0	0	0	2
Other (timing uncertain):					
Height on or below 3rd centile	30	10	8	3	9
Head circumference on or above 97th centile	10	4	3	2	1
Epilepsy	9	0	5	2	2
Behaviour problems	21	2	13	2	4
Three or more minor malformations	10	2	3	2	3
Incoordination	42	4	27	4	7

children with IQs of more than 70, eight (11%) had behaviour problems, compared with 11 (12%) of those with IQs of less than 70 (two children were not tested).

Ten survey children (6%) had three or more dysmorphic features unrelated to chromosome abnormalities or recognised syndromes. In the control group the corresponding frequency was two of 55 (4%).

Forty two children (25%) had incoordination, four of whom had no other risk factors identified. Twenty seven had known risk factors: chromosome abnormality (n=5), a recognised syndrome (n=2), microcephaly (n=3), congenital adrenal hyperplasia (n=1), perinatal stress (n=13), meningitis (n=1), head injury (n=1), and status epilepticus (n=1). Incoordination was not a feature in the two boys with XXY, the girl with the X-autosome translocation, and two of the three children who had infections of the central nervous system. Four of the control children (7%) had incoordination.

Parental education

Parental educational problems were defined as attendance by the parent at a school for the mildly mentally retarded, or an admission of illiteracy or semiliteracy. For a child to be designated as having parents with educational problems, such a history was required from both parents. There was a history of educational problems in the parents of 86 children. Table 4 shows the incidence of parental education problems in children with known risk factors, those with a single possible risk factor, those with two or more possible risk factors, and those in whom no medical features were identified. The percentage of parents with educational problems was lowest in the first of these groups (39%), and highest in the last (77%). Eight children with parents of average or superior education had no medical features identified in their history or examination, and a further 17 had just one possible risk factor.

Table 4 *Medical features and parental education of 169 mildly mentally retarded children*

	No of children	*No (%) of children of whom both parents had educational problems*
Features of known aetiological importance (with or without other possible risk factors)	71	28 (39)
Two or more possible risk factors	26	11 (42)
One possible risk factor	37	20 (54)
No medical features	35	27 (77)
Total	169	86 (51)

Discussion

The attribution of mild mental retardation to medical factors is fraught with difficulties. There is no good working definition of the phenotype, many of the relevant medical factors are open to subjective interpretation, and control data are inadequate, especially in the rapidly changing specialty of perinatal care. Despite these difficulties it is an area requiring medical study. Parents generally appreciate a medical 'label', and genetic counselling may be important. Recent study of the fragile X syndrome[7 8] has shown that medical factors are not confined to severely retarded children. It has often been assumed that most mild retardation is multifactorial. If the distribution of IQs was normal, 3% of the population could be expected to have IQs of less than 70. We found that 2% of the Southampton schoolchildren aged 7–11 were attending schools for the mildly mentally retarded at the time of our survey, but only half of these were in the IQ range 50–70. The factors apart from IQ that influence referral for this type of special education are not clear. Parental approval is required, and referral must be to some extent dependent on facilities for remedial education available in normal schools. We expected (but did not find) that children with IQs of over 70 would be more likely to have behaviour problems. Selection could bias the study sample either towards or away from identifiable medical causes.

Over a quarter of the children in the schools for the mildly mentally retarded were not included in the survey. Parents of 31 children actively declined to take part and although no reason for refusal was sought two explained that this was because their children had already been thoroughly investigated, and a further nine stated that they did not wish to submit their children or themselves to venepuncture. Nineteen families did not respond and were not available for two home visits at prearranged times. Sociocultural problems may be important in these families, and their exclusion could have biased the population sample.

The risk factors shown in table 1 are plausible explanations of mental retardation, although some doubt must remain about the individual importance of the perinatal features. Comparison with paired sibling controls showed a significant excess of perinatal problems in the index patients. Some of these are, however, subjective or poorly standar-

dised, and there is always the possibility that perinatal difficulties are secondary. Other factors, including the child's original potential, may reduce or enhance the consequences of early brain damage. Bearing in mind these caveats, perinatal events of the type we have reported must be considered as having potential aetiological significance.[9 10]

Medical factors having a probable association with mild mental retardation were identified in 71 of these children (42%). Hagberg[1] in a study of 91 Swedish children with IQs of 50–70, found similar factors in 43%. From the results of our survey we believe that reduction of the genetic contribution to mild mental retardation by appropriate genetic counselling would not be feasible. The eight chromosomal abnormalities had all arisen de novo, though four of the mothers were over 35 years when the children were born. All children in the survey were born before August 1976. More recently their mothers might have been offered amniocentesis. Three other children had prenatal genetic defects (Sotos' syndrome, Aarskog's syndrome, and congenital adrenal hypoplasia), but in all three the genetic defects became apparent only after the birth of the children. Alcohol fetopathy was found in only one child in contrast with the Swedish study[1] in which 8% of mildly retarded children had the fetal alcohol syndrome.

We have not so far been able to account for the lack of fragile (X) chromosome cases in our sample. Extrapolating from the data of Webb *et al*[7] we should have expected five affected boys in our age group in Southampton, two or three of whom might have been at schools for the mildly mentally retarded, plus perhaps four or five affected girls. The relevant cytogenetic techniques leave scope for variability, but the laboratory did make this diagnosis on samples from other sources during the period of the survey.

Though no firm conclusions could be drawn from the group of 63 children who had possible risk factors alone, certain points emerged. Maternal diabetes was the sole medical feature in three children. Children born to diabetic mothers are at increased risk of physical abnormalities[11] but we are not aware of any previous association with mental retardation. One of these children, who had parents of normal intelligence, had a brother who was also retarded. Thirty children (18%) were of small stature. In two, this could be related to medical conditions (fetal alcohol syndrome and severe pertussis), but in 28 children there was no obvious cause. In 10 children small stature was the only medical feature noted. The association beween small stature and mild mental retardation is not clear, but there may be an interaction between the behavioural attributes of the parents and the child.[12] Incoordination, which featured in 42 children (25%) was associated with known risk factors in 27 (13 with perinatal stress). In contrast, Hagberg[1] found that 43% of mildly retarded children had a neurological abnormality, but does not give details of the method of assessment used.

Children in all the aetiological groups had parents who had had educational problems, but the proportion was highest (77%) in 27 children with no recognised medical risk factors; in 37 children with just one possible risk factor, parents of 20 had had educational problems. Polygenic factors may contribute appreciably to the mental retardation in these two groups of children, but similar findings could be produced by as yet undetected major familial factors such as single gene defects.

We found no previously unrecognised errors of metabolism in the mothers or children in the survey, hence routine biochemical testing would not seem appropriate in the aetiological investigation of children at these special schools. We recommend careful physical examination of the children by school medical officers, looking especially for minor dysmorphic features. Referral to a paediatrician or geneticist should be considered if three or more dysmorphic features are found, or if a genetic syndrome is suspected. We recommend chromosome analysis for all mildly mentally retarded children irrespective of whether there are any dysmorphic features. Finally, in assessing the children account should be taken of the level of parental intelligence and of any possible contributory features in their history, but in some children no cause for the retardation will be found. There were eight children in this survey who had parents of normal intelligence and no medical features identified, and a further 17 (again with normal parents) who had just one feature of uncertain relevance to account for their retardation. It was beyond the scope of this study to investigate these children further, but identification of children with idiopathic mild mental retardation and their further neurological investigation might be of value.

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