ELECTRONIC LETTER

A school based study of children with learning disability indicates poor levels of genetic investigation

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Global learning disability (LD) is a neurodevelopmental defect in the capacity to acquire all or most learned higher mental skills that has a birth incidence of between 0.6% and 8% depending on case definition.¹ LD shows extreme aetiological heterogeneity and can be the result of prenatal (most common and mostly genetic), perinatal (mostly hypoxic-ischaemic), or postnatal (mostly trauma or infective) onset disease processes. A specific diagnosis aids both accurate prognosis and genetic counselling but history and physical examination alone often cannot firmly establish the aetiology. In this situation, the consensus of expert opinion is that chromosome analysis and fragile X DNA testing be performed as minimum laboratory investigations.² We wished to assess the completeness of these basic investigations in a community based population with LD.

SUBJECTS AND METHODS

The study group was 128 children attending two state funded schools in north-east Edinburgh that provide special educational services for children without major physical handicap but with mild-moderate (IQ 50-70) or moderate-severe (IQ <50) LD. School 1 takes children aged 5-12 years and school 2 takes those aged 13-18 years. With written consent, 110 children (85.9%) were studied. They had a mean age of 12.3 years (range 5.8-17.9) and a male:female ratio of 67:43 (table 1). Hospital notes (both paediatric and clinical genetics) and community paediatric and school medical records were reviewed. Cytogenetic and DNA diagnostic reports were independently identified from regional laboratory records. A single clinical geneticist examined all children and a family history was obtained from the child's parent or guardian.

RESULTS

Twenty-six children (23.6%) had a relevant, existing diagnosis (10 single gene disorders, nine chromosomal abnormalities, one multiple malformation syndrome, and six with an environmental or teratogenic cause). Of the remaining 84 children with "learning disability-cause unknown" (LDCU),

Table 1 Basic information on school population

	School 1	School 2	Total
Number attending	55	73	128
No reply	4	3	7
Consent refused	5	6	11
Number examined	46 (83.6%)	64 (87.7%)	110
Male:female ratio	30:16	37:27	67:43
Age range (years)	5.8-13.1	11.9-17.9	5.8-17.9
Mean age (years)	9.75	14.0	12.3

Written consent was obtained for the participation of 87.5% of the children attending both schools. There was no reply obtained after two requests from seven of the parents or guardians. Of the 11 children for whom consent was refused, seven were already known to the clinical genetics services and had definitive diagnoses.

Table 2 Genetic investigations in LDCU cases

	School 1	School 2	Total
Number of LDCU cases	32	52	84
Chromosomes	19 (59.4%)	10 (19.2%)	29 (34.5%)
FRAXA	10 (31.3%)	6 (11.5%)	16 (19%)
Both	9 (28.1%)	4 (7.7%)	13 (15.5%)
LDCU cases with FH	17	29	46
Chromosomes	8 (47%)	7 (24.1%)	15 (32.6%)
FRAXA	4 (23.5%)	5 (17.2%)	9 (19.6%)
Both	2 (11.7%)	4 (23.5%)	6 (13%)

The completeness of basic genetic investigation is documented in all children with LDCU and in the subgroup with an affected first, second, or third degree relative.

chromosome analysis had been performed in 29 (34.5%) and fragile X analysis in 16 (19.0%). In only 13 (15.8%) cases had both investigations been completed (table 2).

No family history was available for one adopted child and the other 83 LDCU cases were from 76 families. Overall, 46/83 (55.4%) LDCU cases (39/76 (51.3%) kindreds) had an affected first, second, or third degree relative. Eighteen families (23.7%) had more than one affected child; 19 of the mothers (25%) and seven of the fathers (9.2%) had LD (defined as having attended a special school). In three families (3.9%), both parents were affected. The rates of genetic investigation were very similar in the groups with and without a family history of LD (table 2). LDCU kindreds with a positive family history were designated at "high genetic risk". Only 6/46 children from these kindreds had both investigations completed. We therefore offered to perform the necessary blood tests on the children from the high genetic risk families in their school using the school medical services. With parental consent, 22/40 (55%) of these children have had follow up tests performed in either school 1 or school 2. Definitive diagnoses have been achieved in 3/22 (13.6%) cases. These were all cytogenetic diagnoses and were: 46,XY,del(9)(p24.1;pter)mat, 46,XX,del(16)(p11.2-p13.11)de novo, and 46,XX,del(22)(q11.22)mat. The deletions of chromosomes 9 and 22 were both inherited from parents with LD.

DISCUSSION

Surprisingly, this appears to be the first reported attempt to assess the completeness of karyotype and fragile X analysis in a community based population of children with LDCU. It is, therefore, impossible to assess how common and widespread the problem of under-investigation is. The poor level of genetic investigation identified in this study may reflect the fact that

Abbreviations: LD, learning disability; LDCU, learning disability-cause unknown

- Conventional cytogenetic analysis and DNA testing for fragile X are considered screening investigations that should be performed in all children with learning disability where the cause is unknown. We have assessed the completeness of these basic genetic investigations in a community based population of 110 children attending special schools in Edinburgh.
- Of the 110 children, 23.6% had an existing diagnosis. In the remaining group, chromosome analysis had been performed in 34.5% and fragile X analysis in 19% with only 15.8% having had both investigations. Over half of this group had an affected first, second, or third degree relative, with 87% of these "high risk" cases having incomplete investigations.
- As a result of these findings, 55% of the high risk cases have had investigations performed in the school setting through the community paediatric services. Chromosome anomalies were found in three (13.6%) of these cases, two of which were familial.
- We conclude that our previous hospital based approach to genetic investigations in learning disability missed a significant number of families with recognisable genetic pathology.

families of children with LDCU are not interested in the aetiology or recurrence risk of the condition. The high participation rate in this study argues against this and suggests there is little or no antipathy within families. The high incidence of LDCU in first degree relatives, which has been a consistent finding in community based studies,^{3,4} is likely to be a source of significant concern within the families. Why then is the rate of basic genetic investigation so low? Family practitioners and paediatricians in Lothian have had open access to chromosomal analysis and fragile X testing for many years under the NHS (that is, free at point of service). It may be the process of service delivery that is flawed. Our practice at this time was to perform all investigations for learning disability at a hospital or clinic based appointment with a community paediatrician or a paediatric neurologist. This appointment may then result in referral to the genetics clinic for further assessment or investigations. It may be that the families were not referred for investigation. It is also likely that families with multiple affected members would have difficulty attending these appointments and these families, who are at the highest risk of recurrence, may be less aware of genetic services.

Whatever the explanation, it appears that our hospital based approach to investigation of LDCU has disadvantaged vulnerable families, who would welcome accurate genetic advice. We have addressed this by instituting a school based approach, which uses existing school medical services that are administered through the department of community paediatrics. The families with a positive family history were prioritised as they indicate those at particularly high genetic risk. The male excess in this report is consistent with all previous studies of LDCU and emphasises the importance of fragile X DNA testing. To date, "in school" blood samples have been performed on over half the families at high genetic risk and these have resulted in definitive cytogenetic diagnoses in >10% of the children tested, two of which were inherited from a parent with learning disability. In conclusion, we suggest that a community based model will be required to ensure that all high risk families benefit from basic diagnostic services as well as recent important developments such as screening for cryptic subtelomeric aneuploidy.⁵

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REFERENCES

- 1 **Roeleveld N**, Zielhuis GA, Gabreels F. The prevalence of mental retardation: a critical review of recent literature. *Dev Med Child Neurol* 1997;**39**:125-32.
- 2 **Curry CJ**, Stevenson RE, Aughton D, Byrne J, Carey JC, Cassidy S, Cunliffe C, Graham JM Jr, Jones MC, Kaback MM, Moeschler J, Schaefer GB, Schwartz S, Tarleton J, Opitz J. Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. *Am J Med Genet* 1997;**72**:468-77.
- 3 **Bundey S**, Thake A, Todd J. The recurrence risks for mild idiopathic mental retardation. *J Med Genet* 1989;**26**:260-2.
- 4 **Wellesley D**, Hockey A, Stanley F. The aetiology of intellectual disability in Western Australia: a community based study. *Dev Med Child Neurol* 1991;**33**:963-73.
- 5 **Knight SJ**, Flint J. Screening chromosome ends for learning disability. Small chromosomal rearrangements may be behind idiopathic learning disability. *BMJ* 2000;**321**:1240.