

Fragile X, iron, and neurodevelopmental screening in 8 year old children with mild to moderate learning difficulties

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Abstract

Objective—To examine the value of neurodevelopmental examination, fragile X testing, iron studies, and other screening procedures in children with mild to moderate learning difficulties.

Design—A cross sectional case-control study.

Subjects—A 34% random sample (n = 130) of children with mild to moderate learning difficulties born between 01/07/83 and 30/06/84 and resident in North and West Belfast. Controls were 130 children without learning difficulties matched for age and geographical area.

Results—The prevalence of mild to moderate learning difficulties in North and West Belfast was 16%; 115 (89%) of the learning difficulties group and 80 (58%) of the control group consented to participate. Children in the learning difficulties group scored significantly lower in neurodevelopmental testing and were more likely to fail their audiometry assessment than controls. Children in the learning difficulties group were also more likely to be anaemic and had lower serum iron and transferrin saturation than controls. No cases of fragile X were identified. Thyroid function tests and urinary amino acids were all within normal limits. There were no significant differences in anthropometry, head circumference, or formal neurological examinations.

Conclusions—Children with learning difficulties are more likely to be neurodevelopmentally immature and iron depleted than controls. Iron depletion should be aggressively sought and treated. The role for routine assessment for fragile X, thyroid function tests, and amino acid chromatography is doubtful.

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Keywords: neurodevelopmental screening; learning difficulties; iron; fragile X syndrome.

Learning difficulties are a common group^{1 2} of disorders with significant long term morbidity in terms of educational achievement, social interaction, and psychiatric disorders.^{3 4} In a previous study we reported that the child health surveillance system does not recognise the majority of these children as being at risk of learning difficulties in the preschool years.⁵ Increasingly paediatricians within school

Table 1 Examinations and investigations performed

Examinations	Investigations
Height, weight, and head circumference	Full blood count
Formal neurological examination	Iron/transferrin saturation
Neurodevelopmental assessment	Fragile X gene probe
Visual acuity	Thyroid function testing
Audiometry	Amino acid chromatography (urine)

health are being asked to assess these children. The role of the paediatrician in this assessment includes the identification of any concurrent medical problems with implications for treatment, long term outcome, or genetic counselling. Exactly how these objectives translate into clinical practice for the milder end of the learning difficulty spectrum is unclear. In this study we examine various options for examination and investigation in order to comment on their value as routine screening measures (table 1).

Children with learning difficulties form a heterogeneous group. Our selection criteria were operational, in that the subjects attended a special school for children with moderate learning difficulties or were significantly behind in normal school. Placement in a school for moderate learning difficulties in North and West Belfast depends on educational psychology assessment. Children with severe learning difficulties, physical handicap (for example, cerebral palsy, hearing or sight impaired, etc), and children with autism or speech and language disorders are placed in other specialised units and were excluded from our study. The children having difficulties at mainstream primary school encompassed the entire spectrum of mild learning difficulties from global delay to specific learning difficulties, with or without secondary behavioural problems. However the majority of these children will not have had formal educational psychiatry assessment and therefore the paediatrician assessing these children cannot use such divisions to base any decisions on screening investigations. The use of straightforward operational criteria makes the translation of the findings of this study into clinical practice easier.

Neuroimmature children are clumsy, often fail at games, and can become socially isolated. These children may be at risk of secondary behavioural problems that can compound underlying learning difficulties. Otitis media with effusion (OME) has been shown to delay a child's acquisition of speech⁶ and the concur-

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Table 2 The neuroimmaturity examination

Gross motor	Pronator drift	Head rotation	Rhomberg's	Heel/toe walk
	Hop	Stands on one foot	Jumps 10" both feet	Fog test
	Pushes to prone	Lateral sitting ability		
Fine motor	Finger/thumb apposition	Finger/nose coordination	Disdiadochokinesia	L/R awareness
Performance skills	2-Dimensional stairs	3-Dimensional stairs		

rent reduction in sensory input may well have a compounding effect on learning potential.^{7,8} The usefulness of visual acuity testing, anthropometry, and formal neurological examination in children with learning difficulties needs clarification.

Screening for the fragile X gene has been suggested for children with severe learning difficulties⁹ but the variability of clinical expression of this gene in both affected males and female carriers,¹⁰ combined with the wide spectrum of learning difficulties seen in our schools leads to difficulties in defining 'high risk' populations.

Iron is an essential cofactor in the synthesis of various neurotransmitters¹¹ and it is now widely accepted that iron depletion can impair cognition and affect.^{12,13} The identification and treatment of iron depletion in children, particularly those with learning difficulties, is therefore essential. The need for other investigations such as thyroid function testing and amino acid chromatography is less clear.

Methods

North and West Belfast is a deprived inner city area with a population of 180 000, served by 60 mainstream primary schools and two schools for children with moderate learning difficulties. The population studied was drawn from all children born between 01/07/83 and 30/06/84 currently attending primary school in North and West Belfast. Children were 7 to 8 years old at the time of the study, ensuring a minimum of two years of full time primary school education to facilitate detection of significant learning difficulties by their teachers. Children were excluded if the school they attended refused to participate in the study, if they attended a school for severe learning difficulties, or if they were known to have a physical problem likely to contribute to or mimic learning difficulties, such as moderate to severe sensorineural deafness, severe visual handicap, or a recognisable syndrome.

Mild to moderate learning difficulties were defined in any child in mainstream education requiring remedial assistance because of being two or more years behind in one or more subjects, or any child attending a school for moderate learning difficulties.

Sixty schools with 2561 eligible children participated in our initial study.⁵ The prevalence of learning difficulties was 16% (408 children). Three hundred and eighty seven children were receiving remedial help at mainstream primary schools and 21 children were attending MLD (moderate learning difficulties) schools.

The study group comprised a sample of 130 children from 30 different schools selected at random from the 408 children with learning difficulties. This group was stratified to include all 21 children attending the MLD schools.

The control group comprised a random sample of 130 classmates from five different schools who were felt by their teachers not to have significant learning difficulties.

A letter was sent to the child's principal carer through the principal for permission to examine and investigate their child. A second letter detailing the nature of the examination and investigations was then sent directly to the home address.

The children were examined in their primary school. A nurse checked an audiogram, visual acuity, height, and weight. The principal author then performed a formal neurological and neurodevelopmental assessment.

The neuroimmaturity assessment (table 2) concentrated on motor skills and aimed at identifying children with significant clumsiness who might be at risk of secondary behavioural problems. It was not a complete neurodevelopmental assessment and no attempt was made to score language delay, social skills or other aspects of neurodevelopment. It consisted of 12 items as described by Peters¹⁴ with, in addition, shoulder girdle stability, as assessed by pushing from prone to a straight arm 'press up' position, and lateral sitting position, to determine cross lateralisation problems. Two and three dimensional stair building¹⁵ were also included as tests of performance ability. Each item was scored as 0, 1+, 2+, 3+, or 4+ according to the degree of deviation from normal (0 being normal and 4+ maximum deviation). Scores were then dichotomised to pass (0 to 1+) and fail (2+ to 4+). A neuroimmaturity score for each child was calculated as a percentage:

$$\frac{16-X}{16} \times 100$$

where 16 = total number of tests and X = number of failed tests.

Finally each child had blood taken for fragile X screening, thyroid function tests, haemoglobin, and iron studies, and urine was obtained for amino acid chromatography. For the control group the examination remained the same but investigations were limited to iron studies and haemoglobin.

Anaemia was defined as a haemoglobin less than 115.0 g/l¹⁶ and iron deficiency as serum iron less than 11 µmol/l and/or transferrin saturation less than 16%.¹⁷ All children identified as iron depleted were contacted and a course of iron treatment prescribed through their general practitioner.

STATISTICS

As we were using a ranking scale to score the neurodevelopmental examination non-parametric analysis (the Mann-Whitney U test) was used. Group comparisons of iron serology involved parametric analysis. Comparison of binomial data such as the results of audiometry used χ^2 testing.

Table 3 Examination findings in learning difficulties and control groups

Examination	Learning difficulties (n=115)	Controls (n=63)	p Value
Gross motor, median (range)	87.5 (25-100)	95 (70-100)	< 0.0001
Fine motor, median (range)	87.5 (25-100)	97 (56-100)	< 0.0001
Performance, median (range)	75 (0-100)	100 (25-100)	0.0001
Failed audiometry	35	5	0.0006

Table 4 Investigation findings in learning difficulties and control groups

Investigation	Learning difficulties (n=104)	Controls (n=80)	p Value
Anaemic (%) with haemoglobin < 115.0 g/l	12 (11)	1 (1.2)	0.007
Iron depleted (%) iron < 11 µmol or saturation < 16%	20 (19)	7 (9)	0.05
Haemoglobin g/l, mean (SD)	123.0 (7.0)	128.0 (7.0)	< 0.0001
% Saturation, mean (SD)	24 (8.4)	27.8 (8.4)	0.002
Iron (µmol/l), mean (SD)	14.5 (5.1)	17.1 (8.0)	0.01
Fragile X detected	No cases	NA	
Abnormal TFTs	No cases	NA	
Abnormal amino acid chromatography	No cases	NA	

TFTs = thyroid function tests.

Results

Of the 130 children in the study group, 115 (88%) agreed to examination and 104 (80%) to investigation. Of the 130 children in the control group, 63 (48%) agreed to examination and 80 (61%) to investigation.

Children in the learning difficulties group were significantly more likely to score lower in neurodevelopmental testing and fail their audiometry assessment than the controls (table 3). There were no significant differences in anthropometry, visual acuity or head circumference. Formal neurological examination confirmed one child with a known mild hemiplegia.

DNA was cultured successfully in 95 children (74%), 56 boys and 39 girls. No cases of fragile X were identified. Children in the learning difficulties group were more likely to be anaemic (11% *v* 1%, *p* = 0.007) and had lower serum iron (14.5 *v* 17.1, *p* = 0.01) and transferrin saturation (24 *v* 28, *p* = 0.002) than the controls. Thyroid function tests and urinary amino acids were all within normal limits (table 4).

Discussion

The move towards a combined child health service and evidence-based medicine has resulted in different work practices within both community and hospital. The impact of these changes has been seen especially in educational medicine. Population screening has been directed away from secondary paediatric services towards primary care and has been replaced by a more focused selective screening approach. There is an increasing awareness of areas of unmet needs that have previously been unrecognised by the health services¹⁸ such as the child with mild to moderate learning difficulties. Historically these children have been viewed as a purely educational consideration; however, presently the role of medical investigation, assessment, and treatment for these children is under debate. Many of the recommended approaches to children with learning difficulties have been developed by paediatricians exposed to the more severe end of the learning difficulties spectrum and may not be applicable to this group.

The lower scores in neuroimmaturity assessment of the learning difficulties group reflect the association of learning difficulties and neurodevelopmental delay.^{15, 19} Children who perform badly at tasks of coordination are at risk of social alienation by their peers and this may lead to secondary behavioural problems that can contribute further to academic failure. The therapeutic value of a short intensive course of occupational therapy needs formal evaluation but is considered useful by many therapists. Where there is significant clumsiness, especially if accompanied by behavioural problems or academic failure, appropriate referral should be considered. The wide overlap of scores between children with learning difficulties and controls is important and emphasises previous research that the neurodevelopmental assessment is unlikely to be useful as a primary screening tool in detecting learning difficulties.¹⁵

Although the failed audiometry assessments do not mean that these children satisfy the diagnostic criteria for OME, it does suggest that as a group they would be at increased risk of such problems which may contribute to learning difficulties^{7, 8} and as such would warrant aggressive detection and treatment.

The failure of this study to detect any cases of the fragile X gene would suggest that until larger studies are completed on similar populations, fragile X screening of children with mild to moderate learning difficulties should not be recommended. The finding of significantly more cases of anaemia and lower iron stores is a cause for concern. Iron depletion, with or without coexisting anaemia, is associated with developmental slowing in infants and mood changes and poor concentration in children.^{20, 21} These effects are at least partially reversible.²² While iron depletion is unlikely to be the single aetiological factor in children with learning difficulties, it may be a significant contributory problem and deserves identification and treatment. Iron depletion may also act as a marker for other nutritional deficiencies.²³ As in the case of fragile X screening, the need for amino acid chromatography or thyroid function testing would seem to be limited in the absence of other clinical concerns.

CONCLUSION

Children with learning difficulties are more likely to be iron depleted, to fail audiometry assessments, and to score poorly on tests of neuroimmaturity than controls. These findings have important implications for the community paediatric team assessing children with significant learning difficulties. Iron depletion and OME should be carefully sought and aggressively treated. Also children with coexisting neuroimmaturity, especially if associated with evidence of secondary behavioural problems, need to be identified and consideration given to occupational therapy assessment and treatment. The role for routine assessment for the fragile X gene, thyroid function tests, and amino acid chromatography is questionable, particularly in the light of the existing neonatal screening programme for hypothyroidism and

aminoacidurias. It may be reasonable, especially if these findings were supported by further studies, to restrict some of these tests to cases with clinical or historical markers that raise the clinician's index of suspicion.

The assessment of all children with mild to moderate learning difficulties referred to the North and West Belfast community paediatric team includes a detailed history and examination, an examination or occupational therapy assessment to detect significant neuroimmaturity, audiology assessment for OME, and iron studies plus haemoglobin estimation. Because of the treatable nature of thyroid dysfunction, thyroid function tests continue to be included until larger studies are forthcoming. Screening for fragile X and aminoacidurias is restricted to those children with either more severe learning difficulties or other positive clinical markers.

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