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

N Corrigan, M Stewart, M Scott, F Fee

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 participation. 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.

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.

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

Learning difficulties are a common group\(^2\) of disorders with significant long term morbidity in terms of educational achievement, social interaction, and psychiatric disorders.\(^3\) 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 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 counseling. 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).

<table>
<thead>
<tr>
<th>Examinations</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, weight, and head circumference</td>
<td>Full blood count</td>
</tr>
<tr>
<td>Formal neurological examination</td>
<td>Iron/transferrin saturation</td>
</tr>
<tr>
<td>Neurodevelopmental assessment</td>
<td>Fragile X gene probe</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>Thyroid function testing</td>
</tr>
<tr>
<td>Audiology</td>
<td>Amino acid chromatography (urine)</td>
</tr>
</tbody>
</table>

Table 1 Examinations and investigations performed

North and West Belfast
Community Paediatric Unit, Belfast, Northern Ireland
N Corrigan
M Stewart

Queens University
Belfast Department of Epidemiology and Public Health, Belfast, Northern Ireland
M Scott

Belfast Education and Library Board,
Belfast, Northern Ireland
F Fee

Correspondence to:
Dr N P Corrigan,
Altnagelvin Area Hospital,
Londonderry, N Ireland
BT47 1SB

Accepted 19 November 1996
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 Peters'10 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 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 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 Peters'10 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 second letter detailing the nature of the examination and investigations was then sent directly to the home address.

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 Peters'10 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 second letter detailing the nature of the examination and investigations was then sent directly to the home address.

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 Peters'10 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 second letter detailing the nature of the examination and investigations was then sent directly to the home address.

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 Peters'10 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:
Table 3 Examination findings in learning difficulties and control groups

<table>
<thead>
<tr>
<th>Examination</th>
<th>Learning difficulties (n=115)</th>
<th>Controls (n=62)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor, median (range)</td>
<td>87.5 (25-100)</td>
<td>95 (70-100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fine motor, median (range)</td>
<td>87.5 (25-100)</td>
<td>97 (56-100)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Performance, median (range)</td>
<td>75 (0-100)</td>
<td>100 (25-100)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Failed audiometry</td>
<td>35</td>
<td>5</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Table 4 Investigation findings in learning difficulties and control groups

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Learning difficulties (n=110)</th>
<th>Controls (n=80)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemic (%) with haemoglobin &lt; 115.0 g/l</td>
<td>12 (11)</td>
<td>1 (1.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Iron depleted (%) iron &lt; 11 µmol or saturation &lt; 16%</td>
<td>20 (19)</td>
<td>7 (9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Haemoglobin g/l, mean (SD)</td>
<td>123.0 (7.0)</td>
<td>128.0 (7.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Saturation, mean (SD)</td>
<td>24.8 (4.4)</td>
<td>27.8 (8.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Iron (µmol/l), mean (SD)</td>
<td>14.5 (5.1)</td>
<td>17.1 (8.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Fragile X detected</td>
<td>No cases</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Abnormal TFTs</td>
<td>No cases</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Abnormal amino acid chromatography</td>
<td>No cases</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

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 need that have previously been underestimated by the health services14 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 neuromaturity assessment of the learning difficulties group reflect the association of learning difficulties and neurodevelopmental delay.15 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 difficulties7 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.22 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.22 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 neuromaturity 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 neuromaturity, especially if associated with evidence of secondary behavioural problems, need to be identified and considered 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

Corrigan, Stewart, Scott, Fee
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.
