Physical Characteristics of Young Boys With Fragile X Syndrome: Reasons for Difficulties in Making a Diagnosis in Young Males

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Fragile X syndrome is the leading form of hereditary mental retardation, but the condition is still underdiagnosed in young children. Because of concern that the fragile X phenotype is subtle in young boys and therefore contributes to underdiagnosis of the disorder, we evaluated 73 boys (36 with fragile X and 37 same-age boys who were fragile X negative) using a checklist that we devised to learn which characteristics might be the most useful for alerting professionals to this diagnosis. After a multiple comparisons adjustment, only 4 of 42 characteristics differed significantly in their distributions between the two groups of boys ($P < 0.0012$), but 10 other items may also have predictive value for fragile X syndrome ($P < 0.01$). Four additional items occurred in at least 80% of boys with fragile X and may also be helpful for the clinician. Professionals who work with developmentally delayed children should be aware of these 18 clinical characteristics and some of the behavior characteristics commonly seen in boys with fragile X so that they can readily diagnose patients. Am. J. Med. Genet. 92:229–236, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: fragile X syndrome; prepubertal boys; physical characteristics

INTRODUCTION

Over the past 20 years, fragile X syndrome has emerged as the leading known form of hereditary mental retardation and autism [Hagerman, 1996]. This genetic disorder is thought to affect about 1 in 1,500 to 1 in 4,000 males [Tarleton and Saul, 1991; Turner et al., 1996]. The syndrome is associated with a fragile site at Xq27.3 and an abnormality of the FMR-1 gene (fragile X mental retardation-1 gene) at the same site [Rousseau et al., 1991; Verkerk et al., 1991; Vincent et al., 1991; Yu et al., 1991; Bell et al., 1991]. The most important clinical abnormality associated with the FMR-1 gene is mental retardation, but fragile X syndrome may also be associated with aberrant behaviors and an abnormal physical appearance [Hagerman, 1996]. Many studies have attempted to characterize the behavioral and physical phenotype of fragile X syndrome to help clinicians recognize this disorder [Hagerman, 1992; Butler et al., 1991a, b, 1992; Meryash et al., 1984; Partington, 1984; Pulliam et al., 1988; Stevenson and Prouty, 1988; Rimland, 1984]. To our knowledge, however, few studies have specifically addressed the physical characteristics of young boys with fragile X [Thake et al., 1985; Hockey and Crowhurst, 1988; Simko et al., 1989; Hagerman, 1992; Lachiewicz, 1992].

Some of the main physical traits described in men include a broad forehead, an elongated face, large prominent ears, strabismus, hand calluses, a pectus excavatum, mitral valve prolapse, flat feet, macroorchidism and dermatoglyphic abnormalities [Meryash et al., 1984; Chudley and Hagerman, 1987; Storm et al., 1988; Hagerman et al., 1991; Butler et al., 1992; Maino et al., 1992; Hagerman, 1996; Hatton et al., 1998]. Behavior characteristics include: abnormal language (especially perseveration and fast speech), poor eye contact, hand flapping, tactile defensiveness, and impulsivity [Lachiewicz et al., 1994b]. Other behaviors that have been widely reported include hyperactivity, aggression, anxiety and hand biting [Hagerman, 1992, 1996]. Up to 15% of males with fragile X may also carry a diagnosis of “autism” but these findings vary from...
Hagerman et al. [1991a] reported that six anthropometric variables could discriminate 34 males with fragile X syndrome from 71 mentally retarded males without fragile X syndrome at an overall correct classification rate of 97%. These variables were: testicular volume, ear width, bizygomatic diameter, head breadth, plantar crease, and hyperflexibility. Pulliam et al. [1988] reported that the craniofacial characteristics that distinguished fragile X males from controls were elongated face, prominent jaw, simple helix and simple antihelix. Other researchers have used more modest criteria for their screening purposes and have found that higher checklist scores will increase the chance that an individual will have fragile X [Hagerman et al., 1988; Nolin et al., 1991; Laing et. al., 1991]. Although all of this information can lead to forward stepwise discriminant analysis of the subjects based on six of the variables that were: plantar crease, a simian crease, hyperextensible metacarpophalangeal joints, large testes, large ears, and a family history of mental retardation. In another article, Butler et al. [1991a] reported that six anthropometric variables could discriminate 34 males with fragile X syndrome from 71 mentally retarded males without fragile X syndrome at an overall correct classification rate of 97%. These variables were: testicular volume, ear width, bizygomatic diameter, head breadth, plantar crease, and hyperflexibility. Pulliam et al. [1988] reported that the craniofacial characteristics that distinguished fragile X males from controls were elongated face, prominent jaw, simple helix and simple antihelix. Other researchers have used more modest criteria for their screening purposes and have found that higher checklist scores will increase the chance that an individual will have fragile X [Hagerman et al., 1988; Nolin et al., 1991; Laing et. al., 1991]. Although all of this information can lead to increasing numbers of males being appropriately diagnosed with fragile X, some young boys with fragile X do not appear to have many abnormal manifestations (Fig. 1). Physicians have been cautioned to consider fragile X testing on all boys with mental retardation of unknown etiology [Hagerman et al., 1991].

The purpose of this study was to review physical characteristics of young boys with fragile X compared to a control group to learn how much the appearance of these boys differed from other boys whom we screened for fragile X and to learn whether boys with fragile X were likely to display the same physical abnormalities as adult males. We hoped this study would further define some of the main physical features associated with fragile X so that boys with fragile X would be easier for clinicians to identify.

**METHODS**

We devised a checklist to look systematically at some behavioral and physical characteristics of young boys with fragile X as they were evaluated in a child development unit. The checklist consisted of items that had been observed in our own patient population and other items that had been described in previous studies of individuals with fragile X. The checklist was designed to be moderately comprehensive but also useful in the multidisciplinary setting where several other evaluations would be occurring on the same day. This process necessitated that the physical examination be somewhat limited because children with fragile X are often fearful of physicians. We did not want the physical examination to upset the child for subsequent evaluations. The checklist had several sections including a behavioral questionnaire, a medical history section, a family history section and a physical examination section. IQs were recorded. The findings from the behavior questionnaire have been described as part of a previous study and abnormal behaviors were found in five general areas: tactile defensiveness, abnormal language, hand flapping, poor eye contact, and poor self-control (impulsivity) in the fragile X boys [Lachiewicz et al., 1994]. This report describes the findings from the physical examination portion of the checklist and also considers elements of the medical history and family history.

The medical history included information about whether or not the boy had a history of hernias, allergies, eye problems, ear infections, seizures, curvature of the spine, cleft lip or cleft palate. All parents provided a birth weight and 57/73 provided a birth length. Few parents knew the birth head circumference so this item was eliminated.

A family history was elicited to learn if there was a history of mental retardation, fragile X, “autism,” or learning disabilities. Several families presented to our clinic to have their developmentally delayed child evaluated specifically because there was a family history of developmental disabilities, but the family histories were not always conclusive for X-linked disorders. All family histories of mental retardation, fragile X, or “autism” were considered positive, but vague concerns about developmental disorders in relatives were not counted as positive.

All physical examinations were completed by the first author (AML) and focused on basic physical characteristics and other traits often described as abnormal.
in young boys with fragile X. Testicular volumes were estimated using Prader orchidometer beads (Seritek, Inc., Carlstadt, NJ). Testicular volumes greater than 2.5 ml were considered larger than the mean [Hall et al., 1989; Lachiewicz and Dawson, 1994].

One item “adverse response to touch on the skin” was included to learn more about the tactile defensiveness that is frequently described in males with fragile X syndrome. The item was usually completed after the physical examination and referred to how well the child could tolerate the amount of touch involved in the physical examination. Many boys with fragile X seemed especially tactilely defensive during the examination of the ears, heart, hands, feet, or genitalia. This finding generally contributed to a difficult examination when it was present and was the main reason why an abbreviated examination was necessary. Metacarpophalangeal joints were considered somewhat hyperextensible at about 80 degrees and markedly hyperextensible beyond 90 degrees. Flat-footedness was assessed with the child barefooted and in a standing position. The hallucal crease referred to a well-delineated crease between the first and second toe that was at least one centimeter in length. Several items assessed oral-motor skills, but many of the younger boys were unable to respond to these items. These items included licking the lips, moving the extended tongue from side to side, and repeating “puh-tuh-kuh” and “linoleum.” If a boy did not seem able to understand one of these requests, that item was not included in the data analysis. Similarly, the boys were asked to close their eyes on command to examine muscle control of the face. If the boy did not seem to understand the request, the item was not included in the data analysis.

A few physical characteristics previously described in males with fragile X were not chosen for this study including epicanthic folds, dental crowding, and a large and prominent jaw because they are rarely seen in our pediatric population of boys with fragile X [Shellhart et al., 1986; Chudley and Hagerman, 1987; Hockey and Crowhurst, 1988; Pulliam et al., 1988; Meryash et al., 1994; Hagerman, 1996]. Some characteristics such as abnormal dermatoglyphics were omitted because so many of the boys were tactically defensive and did not tolerate touching of the hands and fingers [Simpson et al., 1984, 1986]. “Broad head” (as opposed to a broad forehead) and a vertical mid-sole crease (as opposed to a hallucal crease that begins between the first and second toe) were not included because, at the time that the study began, we were unaware that they might occur frequently in individuals with fragile X [Meryash et al., 1984; Simko et al., 1989; Butler et al., 1991b; Butler et al., 1992].

Several different types of responses were required for the particular items that were included. Some items such as height or weight required a specific measurement. Others, such as the presence of hand calluses had simple yes/no responses. Many subjective items had three possible answers (marked, somewhat, and absent) to help quantify the findings. “Somewhat” was included to allow for a positive response for some characteristics like a broad forehead, an elongated face, and a pectus excavatum when a “yes” answer would have been too positive of a response.

**Subjects**

The 36 subjects and 37 controls ranged from 2.2–10.2 years of age (mean age of subjects = 6.2 years, SD = 2.4 years; mean age of controls = 6.0 years, SD = 2.0 years).
Statistical Methods

For binary traits (yes/no answers), Fisher exact test was used to evaluate possible associations between fragile X status and the presence of the characteristic. When traits were rated on a trichotomous scale (marked/somewhat/absent), associations with fragile X status were initially assessed using the three-level categorization via standard chi-square tests. In those cases where small numbers brought the validity of the chi-square approximation into question, an exact procedure was used [Pagano and Halvorsen, 1981].

These relationships were also evaluated by considering associations with presence of the characteristic to a marked degree only and with presence of any degree of the trait (i.e., collapsing of the “somewhat” category with either the marked or absent categories) and using the Fisher exact test. Because little difference in results was observed among these approaches, we elected to report the combined results of marked and somewhat designations vs. absence of the abnormal characteristic.

Comparisons of quantitative measures (i.e., height, weight) by fragile X status were made using the Wilcoxon rank sum procedure. Where covariate adjustment was required, multiple regression procedures were used to adjust for the effects of age in the comparison of height and head circumference and for the effects of age and height in the comparison of weight among fragile X positive and negative boys. Standard validation procedures were used to assess the appropriateness of the fits and the validity of model assumptions. Adjustment for multiple comparisons was made using the Bonferroni method in conjunction with an overall 5% level of statistical significance [Neter and Wasserman, 1974]. Because of the large number of items analyzed, P-values <0.0012 (0.05/42) were considered statistically significant. P-values <0.01 were considered to indicate suggestive trends. Odds ratios were also reported for the items when there was a significant difference between the two groups or when a trend was noted.

RESULTS

Height, weight, and head circumference did not differ between the two groups when standard regression techniques were used to adjust for age and, in the case of weight, to adjust for height and age. There was no significant difference in mean birth weight, that was 3800 g in the 36 boys with fragile X boys (range 2353–5103 g; SD = 594 g) compared to 3542 g in the 37 controls (range 879–5443 g; SD = 823 g), (P-value = 0.095). There was no significant difference in mean birth length that was 54.6 cm in 29 boys with fragile X (range 48.3–59.7 cm; SD = 3.0 cm) compared to 52.8 cm in 28 controls (range 45.7–60.1 cm; SD = 3.3 cm), (P-value = 0.42).

Of the other 37 items, 4 differed significantly between the two groups: adverse response to touch on the skin; difficulty touching the tongue to the lips; soft skin over the dorsum of the hand; and hallucal crease (Table II). Ten items were suggestive including: a previous diagnosis of mental retardation; a family history of developmental disabilities; an elongated face; gaze avoidance/poor eye contact; ear length >75th centile; difficulty moving the extended tongue from side to side; hyperextensible metacarpophalangeal joints; hand calloses; testicular volume > mean for age; and brisk deep tendon reflexes. The other 23 items did not differ significantly between the two groups.

Four additional items were seen in over 80% of the boys with fragile X and may also contribute to making a diagnosis even though some of these characteristics were also seen frequently in the controls (Table II). These included head circumference greater than the 50th centile (81%), highly arched palate (94%), and difficulty pronouncing “linoleum” (86%). A history of greater than five ear infections occurred in most affected boys (97%), but may not be as helpful diagnostically because it was a prevalent problem in the controls as well (92%).

DISCUSSION

As many previous adult studies have suggested, males with fragile X often have manifestations that can contribute to making a diagnosis of fragile X. In this study only 4 out of 42 characteristics studied differed enough from controls to reach significance after adjustment for multiple comparisons. These included adverse response to touch on the skin (tactile defensiveness), difficulty touching tongue to lips (oral-motor incoordination), soft skin over the dorsum of the hands, and hallucal crease. Three of these items are somewhat subjective but may be useful to clinicians. Ten items showed a trend toward significance and a possible role in discrimination is suggested. Four additional items were seen in more than 80% of males with fragile X, but were also commonly seen in the control population.
Overall, the findings are fairly consistent with previous studies regarding physical characteristics of adults and children, and knowledge of these characteristics should help clinicians recognize fragile X syndrome. One clear difference between the adults and children was that testicular enlargement does not seem to be very useful clinical characteristic for pediatricians until the child is 8 eight years of age [Lachiewicz and Dawson, 1994]. Verbal perseveration may also be difficult to appreciate until a child has relatively good language skills. We did not see an increased incidence of the simian crease in this sample.

As in other studies, no important characteristics such as hand calluses were seen in high percentages in fragile X males and in low percentages of controls. This lack of powerful clinical markers limits the potential of a simple checklist to screen for fragile X. We believe that physicians should continue to follow current rec-

### TABLE II. Clinical Characteristics of Young Boys With Fragile X Syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fragile X positive (% positive (# positive/total number))</th>
<th>Fragile X negative (% positive (# positive/total number))</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Odds ratio&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Four characteristics that were significantly different between the two groups</strong>&lt;sup&gt;d&lt;/sup&gt; and 10 characteristics that were a trend&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Hallucal crease</td>
<td>82.9 (29/35)</td>
<td>29.7 (11/37)</td>
<td>0.0001&lt;sup&gt;d,g&lt;/sup&gt;</td>
<td>11.4</td>
</tr>
<tr>
<td>Adverse response to touch on the skin</td>
<td>61.1 (22/36)</td>
<td>18.9 (7/37)</td>
<td>0.0003&lt;sup&gt;d,g&lt;/sup&gt;</td>
<td>6.7</td>
</tr>
<tr>
<td>Difficulty touching tongue to lips</td>
<td>75.9 (22/29)</td>
<td>27.6 (8/29)</td>
<td>0.0005&lt;sup&gt;d,g&lt;/sup&gt;</td>
<td>8.3</td>
</tr>
<tr>
<td>Soft skin over dorsum of hand</td>
<td>100.0 (35/35)</td>
<td>73.0 (27/37)</td>
<td>0.001&lt;sup&gt;e&lt;/sup&gt;</td>
<td>—&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Elongated face</td>
<td>83.3 (30/36)</td>
<td>45.9 (17/37)</td>
<td>0.0013&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.7</td>
</tr>
<tr>
<td>Family history of disabilities including fragile X, autism, mental retardation and learning disabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucal crease</td>
<td>69.4 (25/36)</td>
<td>32.4 (12/37)</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.7</td>
</tr>
<tr>
<td>Ear length &gt; the 75th centile</td>
<td>72.2 (26/36)</td>
<td>35.1 (13/37)</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.8</td>
</tr>
<tr>
<td>Hyperextensible joints</td>
<td>100.0 (36/36)</td>
<td>75.7 (29/37)</td>
<td>0.002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hand calluses</td>
<td>27.8 (10/36)</td>
<td>2.7 (2837)</td>
<td>0.003&lt;sup&gt;e&lt;/sup&gt;</td>
<td>13.8</td>
</tr>
<tr>
<td>Brisk deep tendon reflexes</td>
<td>72.7 (26/36)</td>
<td>37.8 (14/37)</td>
<td>0.005&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.3</td>
</tr>
<tr>
<td>Gaze avoidance/poor eye contact</td>
<td>83.3 (30/36)</td>
<td>51.4 (19/37)</td>
<td>0.006&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.9</td>
</tr>
<tr>
<td>Difficulty moving the extended tongue from side to side</td>
<td>53.6 (15/28)</td>
<td>17.2 (5/29)</td>
<td>0.006&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5.5</td>
</tr>
<tr>
<td>Testicular volume &gt; mean for age</td>
<td>62.9 (22/35)</td>
<td>29.7 (11/37)</td>
<td>0.009&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0</td>
</tr>
<tr>
<td>Previous diagnosis of mental retardation</td>
<td>91.4 (32/35)</td>
<td>64.9 (24/37)</td>
<td>0.0098&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>B. Characteristics that were not significantly different between the two groups</strong>&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly arched palate</td>
<td>94.4 (34/36)</td>
<td>70.3 (26/37)</td>
<td>0.012&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Inability to close eyes on request</td>
<td>14.5 (4/27)</td>
<td>0.0 (0/29)</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>Prominent helices</td>
<td>66.7 (24/36)</td>
<td>40.5 (15/37)</td>
<td>0.035&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of eye problems</td>
<td>45.7 (15/35)</td>
<td>21.6 (4/37)</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>72.2 (26/36)</td>
<td>48.6 (18/37)</td>
<td>0.056&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Difficulty pronouncing “puh-tuh-kuh”</td>
<td>72.4 (21/29)</td>
<td>46.2 (12/26)</td>
<td>0.059&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pectus excavatum</td>
<td>50.0 (18/36)</td>
<td>29.7 (11/37)</td>
<td>0.097&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Head circumference &gt; 50th centile</td>
<td>80.6 (29/36)</td>
<td>62.2 (23/37)</td>
<td>0.12&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Simply formed helices</td>
<td>27.8 (10/36)</td>
<td>13.5 (5/37)</td>
<td>0.157&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Horizontal palmar creases or distal axial triradii</td>
<td>25.0 (9/36)</td>
<td>13.5 (5/37)</td>
<td>0.213</td>
<td></td>
</tr>
<tr>
<td>Curved fifth finger (clinodactyly)</td>
<td>63.9 (23/36)</td>
<td>48.6 (18/37)</td>
<td>0.241&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Mitral click</td>
<td>2.8 (1/36)</td>
<td>0.0 (0/37)</td>
<td>0.307</td>
<td></td>
</tr>
<tr>
<td>Difficulty pronouncing “linoleum”</td>
<td>86.2 (25/29)</td>
<td>73.1 (19/26)</td>
<td>0.315&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of cleft lip/palate</td>
<td>2.8 (1/36)</td>
<td>0.0 (0/37)</td>
<td>0.493&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ocular abnormalities on examination</td>
<td>27.8 (10/36)</td>
<td>21.6 (4/37)</td>
<td>0.595&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of &gt; five ear infections</td>
<td>97.2 (35/36)</td>
<td>91.9 (34/37)</td>
<td>0.615&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Curvature of the spine</td>
<td>5.6 (2/36)</td>
<td>2.7 (1/37)</td>
<td>0.615&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Flat feet</td>
<td>69.4 (25/36)</td>
<td>62.2 (23/37)</td>
<td>0.624&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of hernias</td>
<td>8.3 (3/36)</td>
<td>5.4 (2/37)</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td>History of seizures</td>
<td>8.6 (3/35)</td>
<td>13.5 (5/37)</td>
<td>0.711</td>
<td></td>
</tr>
<tr>
<td>Broad forehead</td>
<td>72.2 (26/36)</td>
<td>67.6 (25/37)</td>
<td>0.800&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of allergies</td>
<td>37.1 (13/35)</td>
<td>32.4 (12/37)</td>
<td>0.805&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>History of curvature of the spine</td>
<td>2.8 (1/36)</td>
<td>2.7 (1/37)</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Percent of boys with the characteristic (number of boys with the characteristic/total number evaluated).

<sup>b</sup>Unadjusted significance probability corresponding to Fisher’s exact test of no association between fragile X status and presence of clinical trait.

<sup>c</sup>Ratio of the odds that an individual has fragile X syndrome given that he has the clinical trait of interest to the odds that he has fragile X given that he does not have the clinical trait of interest (if there were no association between a particular clinical trait and fragile X status, the expected value of the odds ratio would be unity; hence the p-value cited also corresponds to the null hypothesis that the odds ratio is 1).

<sup>d</sup>P < 0.0012: this criterion was based upon application of the Bonferroni adjustment for multiple comparisons in conjunction with an overall 5% level of significance.

<sup>e</sup>P < 0.01 but P > 0.0012.

<sup>f</sup>The odds ratio is zero or infinite if a zero cell or a 100% cell occurs in the cross-classification, e.g., all fragile X positive individuals have the trait (soft skin over dorsum of hand) or none of the controls has a particular clinical trait.

<sup>g</sup>The answers “somewhat” and “marked” were pooled for these analyses.

<sup>h</sup>P < 0.01.
ommendations that young boys with mental retardation be tested for fragile X syndrome with DNA studies. On the other hand, because many children with developmental delays, may be followed in health systems that are not attentive to the issues of children with developmental delays, fragile X checklists with the items noted in this study and in previous studies may be very useful for other professionals, who work with developmentally delayed children (Table IV). Such a checklist could be modified to the appropriate setting, and it could alert school personnel or early intervention specialists to the possibility that the diagnosis of fragile X may have been missed. Boys, who appear suspicious for this syndrome, could then be referred to appropriate specialists. The fact that over 90% of the boys with fragile X in this study have a previous diagnosis of mental retardation suggests that programs that serve children with mental retardation will be the most likely places to ascertain children with undiagnosed fragile X. A small subgroup of boys will also be diagnosed through other programs such as learning disability programs.

Even though there are few excellent markers for fragile X, many of the items that were either significantly different between the two groups or were trends should be studied carefully because they will help clinicians recognize fragile X. For example, although hand calluses from hand biting were only seen in 27% of the boys with fragile X, the incidence was 10 times higher in the fragile X boys than in the controls (2.7% with an odds ratio = 13.8). Other items seen two to three times more frequently in the boys with fragile X such as simple helices or a history of eye problems should also suggest the possibility of fragile X as should items seen in most children with fragile X such as frequent ear infections. Some of the items that distinguished the groups may be too subtle or not very useful such as enlarged testicles. It was very difficult to assess oral-motor abilities in the youngest boys and the oral-motor findings reported here may only be helpful for detecting fragile X in boys who have some verbal skills.

The high number of children with a family history of fragile X and other developmental disabilities points out the importance of diagnosing this condition within known pedigrees and making genetic counseling services available for relatives of individuals identified with fragile X. This study also gave the authors an appreciation for the large number of families with hereditary “autism” and families with individuals who have a wide spectrum of developmental disabilities that are not necessarily X-linked. For example, one woman physician brought in a son with a autism and a daughter with mental retardation. Their FMR-1 DNA studies were negative for fragile X. We were unsuccessful at establishing a cause for the children’s disabilities even though we think that they have a form of hereditary mental retardation. Butler et al. [1991b] also described a high incidence of familial disabilities (41.6% of 154 males) in his control sample.

The final difficulty that presented as an obstacle for trying to develop a checklist is that many developmentally delayed control boys had some of the same medical problems or physical characteristics that are frequently described in males with fragile X. These included: more than five ear infections (97% vs. 92%), clinodactyly (68% vs. 48%), flat feet (69% vs. 62%), and hyperextensible metacarpophalangeal joints (100% vs. 76%). It is unclear why so many children with developmental disabilities have these types of findings but they may be related to low muscle tone or connective tissue defects. Some of these characteristics may be common in all young children.

This study had several limitations that may have biased the results. This study was conducted out of a child development unit that assists children with developmental disabilities. Therefore, all of the subjects and controls had some type of a developmental delay. Whereas comparing boys with fragile X to a sample of normally developing boys might have strengthened the results of the study, we did not think that it was-im-
important to distinguish the physical traits of normally developing boys from those of boys with fragile X because we do not evaluate normal boys for fragile X. On the other hand, that information might be important for clinicians working in general practice. Another limitation was that many families came to be tested for fragile X because there was a family history of developmental delay. This type of referral occurred very frequently when fragile X DNA studies first became available. The number of controls with a family history of developmental disabilities may have been higher in this sample than it would have been in a larger or subsequent sample.

In addition, when this study was conducted, most of our patients with fragile X were Caucasian whereas our other patient populations were more racially balanced. Because we anticipated that all or most of our patients with fragile X would be Caucasian, we only included Caucasian boys as controls. At the present time, we see more African-American children with fragile X and think that this group of patients should also be studied as well. Many of our African-American patients with fragile X have many of the same physical anomalies as are found in Caucasian boys with fragile X.

Another limitation is that we did not use rigorous measurements to determine whether the child had some clinical features such as an elongated face but rather relied on the clinical impression of the examiner. The reason for this was that we hoped to detect physical examination items that would be useful in a wide range of settings. We did not think that using rigorous standards could be duplicated outside of the specialist’s office. In the future, anthropometric measurements would be very useful to confirm some of these findings in children and a few additional items should also be included such as a broad head and plantar creases of the soles.

We hope to validate these findings in another group of boys and apply a multivariate treatment to refine this checklist further. Efforts could then be made to develop a discriminatory instrument. This effort would require a larger sample to develop the classification model, to validate the model, and to evaluate misclassification rates.

Finally, we knew the fragile X status of about half of the boys who were enrolled in this study before their physical examinations. Although a blinded study would have been preferable, most of our patients with fragile X syndrome have already received a diagnosis and they present to our clinic for assistance with behavior and educational concerns.

ACKNOWLEDGMENTS

This project was supported by grants from the North Carolina Council on Developmental Disabilities, the Duke Children’s Miracle Network Telethon, the North Carolina Civitans, the North Carolina Knights of Columbus, and the March of Dimes Social and Behavioral Research Grant 12-195.

REFERENCES


