EVIDENCE-BASED CASE REVIEWS

Investigation of children with "developmental delay"

A 7-year-old boy is referred to you with concerns about developmental delay. On assessment, he is found to have moderate mental retardation (IQ of 50) but no remarkable physical findings. His parents are considering having another child, and they wonder what caused the retardation in their first child and whether it is likely to recur in future offspring.

BACKGROUND

Developmental delay is a common problem in pediatrics, with an estimated population prevalence as high as 10%.[1-4] The etiology includes various genetic and environmental processes, with the most common causes being Down syndrome and the fragile X chromosome. The proportion of children with severe mental retardation found to have an organic cause is reported as 55% to 57%.[5-7] No consensus exists on the choice of investigations for developmental delay, with clinicians using a wide variety of investigations.[8] The example we give in this article is intended to illustrate the process used to evaluate developmental delay in a variety of circumstances, recognizing that the specifics will vary according to the clinical situation.

This scenario raises many clinical questions. You wish to use an evidence-based approach, so you frame your questions to maximize the yield from searching and look first for high-quality systematic reviews and evidence-based practice guidelines to answer your questions. However, because most systematic reviews address issues of therapy, no reviews or guidelines are found that address your questions, which are mostly related to the probability of particular causes of developmental delay. You go to MEDLINE and EMBASE searches to try to answer these questions (box 1).

You want to know the best estimate for the prevalence of fragile X chromosome in the general population and the best estimate for the prevalence of fragile X chromosome among children with learning disabilities. From the 133 articles found in your search, 10 described population-based studies of the prevalence of fragile X chromosome that were performed since the cloning of the fragile X mental retardation gene (*FMR1*) in 1991. Of the 10 studies, only 2 meet most of the criteria for high-quality prevalence studies (box 2).

You decide to start with the study of Murray et al

Summary points

In a 7-year-old child who has moderate intellectual impairment:

- The likely prior probability of having fragile X syndrome is between 1 in 40 and 1 in 250 (ie, to find 1 child with the fragile X chromosome, between 40 and 250 children would need to be tested)
- Currently available evidence shows that when a scoring system based on physical and behavioral features is used, a diagnosis of fragile X syndrome can be confidently ruled out in those with low scores
- Decisions that are made about testing will depend on the population from which the child comes and the values that the tester and the parents put on having a diagnosis versus the disadvantages of unnecessary testing
- The benefits of using this "clinical diagnostic test" include preventing children from being subjected to an unnecessary blood test, sparing parents the anxiety of awaiting the results, and reducing the cost of investigation
- The benefits of testing for the fragile X chromosome include the resolution of diagnostic uncertainty, the prevention of further investigations, and the identification of female carriers

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Down syndrome is one of the more common causes of developmental delay

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Competing interests: None declared

Box 1
Focusing a literature search

- **Baseline risk** In a 7-year-old boy (population) with mental retardation who does not have a diagnosis responsive to specific interventions (exposure), what is the risk of having the fragile X chromosome (outcome)?
  Search: MEDLINE 1966 to present and EMBASE (Winspirs); search terms *fragile X* (text or MeSH heading) *AND prevalence*
- **Baseline risk** In a boy with mental retardation (population) and no dysmorphic features (negative test result), what is the risk of having the fragile X chromosome (outcome)?
- **Baseline risk** In a boy with mental retardation (population) with dysmorphic features (positive test result), what is the risk of having the fragile X chromosome (outcome)?
  Search: MEDLINE (PubMed Clinical Queries); search term *fragile X*—click on "diagnosis" and "specificity"
- **Intervention/therapy** In a boy with mental retardation (population), does knowing the diagnosis of fragile X chromosome (exposure) improve the parents' ability to plan and cope (outcome)?
  Search: MEDLINE (PubMed); search terms *parents AND fragile X/diagnosis*

Box 2
Criteria for appraising the quality of prevalence studies

- Was the case definition clear?
- Was case ascertainment complete?
- Were details of nonresponders or those not tested clear?
- Was the group studied representative of your patient?
- Did prevalence estimates include confidence intervals and take into account the possibility of different disease rates in the nonresponders?

Table 1 *Phenotypic characteristics associated with fragile X: checklist and scoring system**

Characteristics	Score 0	1	2
Mental retardation	IQ > 85	IQ 70–85	IQ < 70
Family history	None	Maternal female with psychiatric disorder	Maternal history of X-linked mental retardation
Elongated face	Not present	Somewhat	Present
Large or prominent ears	Not present	Somewhat	Present
Attention deficit hyperactivity disorder	Not present	Hyperactivity	Present
Autistic-like behavior†	Not present	1 behavior	>1 behavior

*From Giangreco et al.[12]
†Tactile defensiveness, perseverative speech, hand flapping, poor eye contact.

because it was limited to boys, used a population-based sample, and tested only those aged 18 years or younger.[9] Neither the case definition for mental retardation nor the distribution of IQs in the population is stated in the study, and the low prevalence of fragile X chromosome suggests that this is a relatively lower risk group (higher IQ) than that used in other studies. Only 70% of children with special educational needs were tested, and no information is available about nonresponders. Because the prevalence estimate of fragile X chromosome from this study would be affected if children with the chromosome were less or more likely to participate, you try varying the prevalence in the nonparticipating group to half or double that of the participating group. This gives a prevalence range for the overall population of between 1 in 3,990 and 1 in 6,171, which is reassuring because these numbers overlap with estimates from other studies identified by your search (de Vries et al,[10] 1/6,045; and Turner et al,[11] 1/5,000). Applying the same assumptions to the population of learning disabled boys in this study gives a range of 1 in 162 to 1 in 250 (0.6%-0.4%).

In the study by de Vries et al, the learning-disabled group was stratified into mild and moderate-to-severe learning difficulty.[10] Unfortunately, the authors excluded those who already had a diagnosis of fragile X; these cases must be included for accurate prevalence figures. If the prevalence of fragile X chromosome among the nonresponders is similar to that among the responders, then adding those known to have fragile X and new diagnoses to the numerator gives an estimated prevalence of fragile X chromosome for mild mental retardation of 1 in 50, with 1 in 40 for moderate to severe mental retardation. In your 7-year-old child who has moderate intellectual impairment, you estimate the probability of his having the fragile X syndrome as somewhere between 1 in 40 and 1 in 250. You would, therefore, need to test between 40 and 250 children to find 1 child with the fragile X chromosome.

You next consider the usefulness of dysmorphic features in ruling in or ruling out the diagnosis of fragile X syndrome. A search nets 33 articles regarding dysmorphic features in those with the fragile X chromosome. From the abstracts, two articles were found that used a combination of physical and behavioral features to select who, among a group of mentally retarded children, has the highest probability of testing positive for the fragile X chromosome, using molecular testing for the *FMR1* gene.[10,12]

The article by Giangreco et al refines previously defined checklists of phenotypic characteristics associated with the fragile X chromosome into a six-item checklist with a scoring system, shown in table 1.[12]

In this study, a score of 5 or more of a maximum of 12 was found to identify all children who had the fragile X chromosome. Using the identification of these features as a "diagnostic test" for fragile X chromosome, with mo-

Box 3
Criteria for appraising studies of diagnostic tests

- Does the study include an independent, blind comparison with an adequate reference standard?
- Did the sample include an appropriate spectrum of patients to whom the test should be applied in practice?
- Did the test result influence the decision to perform the reference standard?
- What are the results, and what is the precision of the results?
- Will the test help in caring for patients?

lecular testing as the gold standard, you use the guidelines on assessing diagnostic and screening tests summarized in box 3.[13]

In this retrospective study, the molecular polymerase chain reaction (PCR) technique was used in all patients, but the authors do not state whether those applying the diagnostic test were blind to the (PCR-defined) fragile X status of the patients. If the assessors already knew the "answer," the potential for biased assessment is high. The scoring system is clear; however, some of the physical features, such as long face and large or prominent ears, are subjective, and no objective measurements are given. Some of the behavioral characteristics may also be open to interpretation. The provision of genetic testing at the time of the study may have been unique to this study or this location; if so, this could have attracted a highly selected group of children, and the results may not be generalizable. Because the clinical features of fragile X syndrome are well known to clinicians, and all children were referred for testing, the children referred are likely to have had a high prevalence of the chromosome. The data necessary for calculating likelihood ratios (LRs) presented in the article are shown in table 2.

In this study, a negative result (those with a score <5) will effectively rule out a diagnosis of the fragile X chromosome because it is a highly sensitive test. That is, children with a low score on the clinical assessment are unlikely to have the chromosome. However, the calculated LR of a positive test in this study is 2.5. In general, LRs between 2 and 5 generate only small changes in probability. Indeed, if the pretest probability is 3.5%, then a positive test increases the probability of having the fragile X chromosome to only 8.2%.

de Vries et al studied a prospectively collected sample with examiners blind to the fragile X result[10] using a similar scoring system: the phenotypic criteria described by Laing et al.[14] Scores were divided into three groups: low risk, when dysmorphic features suggested another diagnosis; medium risk, in the absence of dysmorphic features; and high risk, in the presence of fragile X chromosome

Table 2 *Calculation of likelihood ratios*

Test score	Positive fragile X PCR test, no. of patients	Negative fragile X PCR test, no. of patients	Likelihood ratios
5	12	129	For positive test: (12/12)/(129/323) = 2.5
<5	0	194	For negative test: (0/12)/(194/323) = 0
Total	12	323	

PCR = polymerase chain reaction

characteristics. This sample contained many adults in whom the phenotype is more characteristic than in children. Despite this, the outcome was impressive. None of the low- or medium-scoring males had the fragile X chromosome, with all those who had the chromosome scoring in the high range. Of course, this did not mean that all of the high scorers had the syndrome. The LR for a high score was 10, and the LR for a low or medium score was 0. The high LR for a positive test confirms your suspicion that the patients in their group showed more distinct features. This indicates how test performance, including LRs, can vary when a test is applied to different groups.

Although neither of these studies is ideal, both show that children who do not have the fragile X chromosome can be correctly identified clinically (decreasing the number of molecular tests that are done) and that having clinically identified features increases the likelihood of a positive genetic test but does not confirm the diagnosis. If our group were similar to that described by Murray et al, with a prevalence of 0.4% (the lowest possible estimate of prevalence), and the diagnostic test performed in the same way as described by Giangreco et al, with an LR of 2.5, the

Table 3 *Considerations for genetic diagnostic testing in developmentally delayed children**

Positive effects	Negative effects
Treatment—such as thyroid replacement therapy if hypothyroid	Harm from testing—the pain of venepuncture or the risk of general anesthetic for some investigations
Genetic counseling—such as discussion of chromosome abnormality with extended family	False-positive and false-negative results
Explanation—for parents and family, even if no treatment identified	Financial costs
Prognostic information	
Research—if an investigation may increase understanding of the mechanisms and/or genetics of the developmental delay	

*From Gringras.[8]

Fragile X syndrome: the benefits of testing include diagnostic certainty. (Courtesy of the Fragile X Society, www.fraxa.org)

posttest probability of having the fragile X chromosome would have increased from 0.5% to 1.0%.[9,12] However, the high sensitivity of the test suggests that instead of testing 250 children before finding 1 child with the fragile X chromosome, you could exclude 150 of those children (60%) from testing with minimal risk of missing a case. de Vries et al suggest that in a group with moderate or severe mental retardation, a higher prevalence may be expected (the highest estimate being 3.3%).[10] Excluding those with a known diagnosis from the denominator gives an estimated prevalence of about 4%, so the posttest probability is, therefore, increased to 10%. Under these circumstances, for every 24 children at risk, 14 could be excluded from testing, and 1 of the remaining 10 would have the fragile X chromosome.

You wonder about the benefit to the parents of knowing their son's diagnosis but are not able to find randomized trials or cohort studies directly relating to the diagnosis of fragile X chromosome. A table is found that provides a framework with the different values associated with making a diagnosis in children with developmental delay (table 3).

Resolution of the scenario

You are now able to estimate the probability of the patient's having the fragile X chromosome as somewhere between 1 in 40 and 1 in 250 and would, therefore, need to test between 40 and 250 children to find 1 child with the chromosome abnormality. If this child has a score of less than 5 for the features described by Giancreco et al, you feel confident in ruling out the chromosome abnormality and not proceeding to molecular testing.[12]

Because there is no well-established treatment option, the direct benefit to the patient of making a diagnosis is marginal. However, the use of this clinical diagnostic test avoids subjecting some children to an unnecessary blood test and spares some parents the anxiety of awaiting the results, as well as the unnecessary expenditure. In addition, the resolution of diagnostic uncertainty can provide much relief and stop further investigations for a cause of developmental delay. As more information on the prognosis of this condition becomes available, parents and patients may benefit from this knowledge. Also, for the parents and relatives, the identification of female carriers may allow an informed choice regarding at-risk pregnancies.

CONCLUSION

Within the limitations of current evidence, some information is now available on the range of the possible prevalence of the fragile X chromosome in different groups, and some understanding of how specific features of the fragile X syndrome may influence your decision making. The decisions that are made depend on the group from which the child comes and the values that the tester and the parents put on having a diagnosis versus the disadvantages of unnecessary testing. In this article, we provide a model for thinking through the issues involved in the investiga-

tion of developmental delay and a way of incorporating evidence into this process. We have chosen a common example to illustrate the process, that of fragile X syndrome, the second most common cause of mental retardation after Down syndrome. The prevalence of a particular disorder in different patient groups will influence the outcome of any diagnostic investigations. This method is generalizable to other causes of developmental delay.

This article was edited by Virginia A Moyer of the Department of Pediatrics, University of Texas Medical Center at Houston. Articles in this series are based on chapters from Moyer VA, Elliott EJ, Davis RL, et al, eds. *Evidence-Based Pediatrics and Child Health.* London: BMJ Books; 2000.

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