Screening for fragile X syndrome: a literature review and modelling study

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Executive summary

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Background

Fragile X syndrome (FXS) is an inherited disorder that causes learning difficulty. The disorder affects an estimated one in 4000 males and one in 8000 females. Affected males are generally unable to live independently, while affected females have learning difficulty but may live independently. There is no cure for FXS. Management of affected individuals is through specific educational and psychosocial interventions and treatment of any clinical symptoms.

There are about 10,000 FXS patients in England and Wales. Since the annual cost to the NHS for managing a moderately affected adult was approximately £20,000 (1995 data), the total annual cost of managing FXS patients can be estimated to be £200 million in England and Wales.

FXS is caused by a mutation of the *FMR1* gene, which is located in the Xq27.3 region of the long arm of the X chromosome. It contains a variable trinucleotide repeat [cytosine–guanine–guanine (CGG)] which can become unstable over successive generations. The number of CGG repeats within a gene will determine whether the individual has a normal allele (<55 repeats), premutation (55–200 repeats) or a full mutation (>200 repeats). All males with full mutation (FM) and about half of females with FM are affected with learning difficulty. People with premutation (PM) are not affected in general. The PM can become unstable on maternal transmission and mothers with PM may have affected children. The risk of expansion from PM to FM depends on the number of CGG repeats in the maternal allele and other factors. The expansion risk from PM to FM is much greater in affected families than in the general population.

Options for population and targeted screening for FXS and carriers have been the focus of two previously published HTA reviews. However, the two previous HTA reports reached contrasting conclusions and recommendations for further research. The different approaches recommended by the two HTA reviews were prenatal screening of all apparently low-risk women, and cascade testing of high-risk women following systematic case finding. This review aims to bring together the findings of the two previous HTA reports.

Methods

We first conducted an assessment of published literature, to bring together and update the findings of two previous HTA reviews. Then efforts were focused on the development of a model (the FXS Model) that could be used to compare the cost-effectiveness of active cascade screening of affected families and population based prenatal screening for FXS. The assumptions about input parameters to the FXS Model were based on a comprehensive literature review and the model's test running.

Major findings

Prevalence

The overall prevalence of FXS was on average 2.3%, ranging from 0.3% to 16% in males with learning difficulty. Preselection according to family history and clinical features can increase the proportion of detected FXS cases among people with learning difficulty who were DNA tested. Using the indirect method and data from eight studies, the prevalence of FXS in the general population was estimated to be 2.3/10,000 (or 1 in 4425).

Pooling data from identified studies (16 for males and 14 for females), the prevalence of PM was 0.16% (1 in 643) among the general male population and 0.67% (1 in 149) among the general female population. These may have overestimated the prevalence of PM in the general population because of the possible founder effect and biased selection in screening programmes. The estimated prevalence of PM was sensitive to the cut-off value of CGG repeat size used to define the PM. The PM repeat sizes in the general population were generally much smaller than those in the affected families.

Risk of expansion from PM to FM

The risk of expansion from PM to FM in maternal transmission is related to the size of CGG repeats

and the risk of expansion from PM to FM in the general population is significantly lower than that in FXS families. Based on data of 1111 maternal PM transmissions, the pooled rate of expansion from PM to FM was 63.4% [95% confidence interval (CI): 60.5 to 66.2%] in PM carriers from FXS families. According to data of 183 maternal PM transmissions, the pooled rate of expansion from PM to FM was 9.8% (95% CI: 5.5 to 14.2%) in PM carriers identified from the general population.

Feasibility and acceptability

The empirical evidence suggested that preconceptual or prenatal screening, case finding and cascade screening are feasible and acceptable by affected families and by the general population. The identified screening programmes were effective in detecting carriers, but a comparison of different strategies was not possible.

Findings of the FXS Model

Simulation results by the FXS Model showed that, over the first 10 years, 4% of PM females and 70% of FM females could be detected by active cascade screening; it is 10% and 58%, respectively, by prenatal screening. The maximal detection rate for FM carriers by active cascade screening is slightly higher than that by prenatal screening (91% versus 71%). However, the maximal rate of detection of female PM carriers by active cascade screening (6%) is much lower than that by prenatal screening (60%). During the first 10 years of simulation, the additional number of births of FXS children that can be avoided each year is estimated to be about 15 (range: 4–31) by active cascade screening, and about 39 (range: 9–76) by prenatal screening.

Due to the fact that the screening candidates need to be tested only once, the total number of women with unknown carrier status will be reduced by the screening programmes. During the first 10 years, the estimated direct cost per year to the NHS in England and Wales is £0.7–0.2 million by active cascade screening and £14.5–9.1 million by a programme of prenatal screening. The incremental cost per extra carrier detected (using current practice as the reference standard) is on average only £165 (range: £129–182) by active cascade screening and £7543 (range: £5316–14,636) by prenatal screening. The incremental cost per FXS birth avoided is on average £8494 (range: £1367–27,314) by active cascade screening and £284,779 (range: £135,510–950,572) by prenatal screening.

Considering that the lifetime care of each FXS patient will cost the NHS about £380,000, the most expensive strategy (population prenatal screening) is still cost-saving in the long term. The estimated net savings per year in England and Wales are about £10 million by active cascade screening and about £8 million by prenatal screening.

Conclusions

The empirical evidence suggested that both prenatal screening and cascade screening are feasible and acceptable. Both prenatal screening and active cascade screening can reduce the number of births of FXS children and are cost-saving in the long term. Population-based prenatal screening is more efficacious and has a greater impact on the population, but it will also cost more than active cascade screening. The active cascade screening of affected families is more efficient, cheaper, but less effective than a population-based prenatal screening.

Since both prenatal screening and active cascade screening have advantages and disadvantages, we believe that both strategies should be evaluated in large-scale trials. It may also be important to explore and evaluate whether and how the different strategies could be simultaneously or sequentially combined.

Publication

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