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Review

Executive summary

An assessment of screening strategies for fragile X syndrome in the UK

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Background

Fragile X syndrome is an inherited form of learning disability that was defined in the late 1970s by cytogenetic detection of an associated fragile site on the X chromosome (Xq27.3). Cytogenetic estimates of the prevalence of fragile X syndrome were as high as 1 in 1039 males but have since been revised downwards. Fragile X syndrome is associated with few medical problems and the subtle physical features make clinical diagnosis difficult. The unusual pattern of inheritance, delineated in the 1980s, was explained once the fragile X syndrome gene (*FMR1*) had been identified in 1991. This gene contains a highly variable repeat of the nucleotide triplet, cytosine–guanine–guanine (CGG). Fragile X syndrome is caused by a large expansion of this CGG repeat (full mutation) that leads to silencing of the *FMR1* gene so no gene product (FMRP) is made. This is the ultimate cause of the learning disability that, in males, is sufficient to preclude independent living.

Family studies show that all individuals with a full mutation inherit it from a female (usually unaffected) who carries either a full mutation or a premutation, a smaller repeat expansion (approximately 55–200 repeats) that is unstable on **female** transmission. The chance of a premutation expanding to a full mutation is positively associated with the size of the repeat (approximately 95% by 90 repeats) but only for female transmissions. When a man transmits a premutation, it remains a premutation; his children are, therefore, unaffected by overt learning difficulties. The potential for population screening or systematic case-finding and extended family testing exists because every unaffected mother of an affected child has a detectable CGG repeat expansion. Reliable prenatal diagnosis is possible in males.

Objectives

To assess the feasibility and acceptability of population screening by addressing the following questions in the context of existing services for families with fragile X syndrome.

- Is there a suitable test for all fragile X genotypes?
- What are the UK population distribution of *FMR1* repeat sizes, and the prevalence of full and premutations in both sexes?
- What reliable information, in terms of the chance of an affected child, is available to women with premutations between 55 and 200 repeats?
- What is the effect of a premutation on the person who carries it?
- What information is available to women with intermediate alleles of 41 to 54–60 repeats?
- How many affected people are diagnosed?
- Given the practice of offering extended family testing (cascade testing), what is the population prevalence of 'as-yet-undiagnosed' female carriers of a full or premutation? What proportion of women at risk can be reached by cascade testing?
- What are the costs of fragile X syndrome to an affected person and their family and to the NHS and society?
- What is the attitude of families to the benefits and costs of a diagnosis of fragile X syndrome, and to the prospect of population screening?
- What data are available from existing population screening programmes?
- What alternatives to population screening exist and are these feasible?

Methods

A key aspect of the review process was to assemble a team with extensive first-hand experience of all aspects of fragile X syndrome, including affected families and the services they use, and a wide knowledge of the relevant literature. They had followed the critical discussions at all the biennial international workshops on fragile X syndrome, including a special session at the 7th International Workshop in 1995 at which an earlier (and substantially different) draft of this report was discussed.

The biomedical literature review of 2429 papers was based on MEDLINE searches, extending to PsycINFO and BIDS for the psychological aspects of [fragile X syndrome] screening. Questionnaire-

based information was obtained from the UK Fragile X Society and data were collected directly from all the regional clinical genetics centres in 1995 and 1998.

Results

Unlike cytogenetic approaches, DNA analysis can reliably determine the *FMR1* CGG repeat number and detect full mutations; however, a combination of polymerase chain reaction and Southern blotting tests is required, which limits high throughput. There are UK population-based data on *FMR1* repeat sizes of up to 60 repeats but insufficient to provide a reliable estimate of the prevalence of premutations (approximately 60–200 repeats). The few data and estimates in the literature of women carriers of the premutation range from 1 in 246 to 1 in 550. Two UK DNA-based estimates of the prevalence of males with the full mutation are 1 in 4090 (Coventry) and 1 in 5530 (Wessex). There are reasonable family-based data for the risk of expansion to a full mutation for the larger premutations but in the 50–69 repeat range the estimates are less secure. This is particularly true of the general population, in which limited screening data (approximately 60 transmissions) produced no full mutation. Women with premutations have about a 16% chance of menopause before 40 years of age compared with approximately 1% in the general population. It was suggested by one study that, in boys with special educational needs, those with an intermediate allele (41–60 repeats) are over-represented.

Probably less than half of those with fragile X syndrome are currently known to UK regional genetics centres. Systematic case-finding, as in New South Wales, Australia, can increase this figure markedly and, coupled with family cascade counselling, can lead to both an increase in reproductive confidence and a 60% reduction in prevalence. Simulations indicate, however, that case-finding and cascade counselling can only reach about half of premutation carriers, although these individuals would include most of those at the highest risk.

The costs of fragile X syndrome are as much social as financial and affected families are generally supportive of the idea of screening. Systematic case-finding and cascade testing are a partial alternative to population screening but require more staff, together with laboratory and other consumables, at regional genetics centres to be feasible.

Conclusions

Programmes of systematic case-finding and cascade testing could achieve benefits for those women most at risk. A trial of systematic case-finding and cascade testing to evaluate the benefits and costs of such an approach would be based on reasonably secure risk figures for counselling. The same is not true for a trial of population screening. The uncertainty about the risks for women from the general population with 55–65 repeats can only be resolved with more research. Ongoing research should clarify a possible link between intermediate alleles and learning difficulties.

Publication

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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