Carrier testing of children for two X linked diseases in a family based setting: a retrospective long term psychosocial evaluation

Outi Järvinen, Anna-Mari Aalto, Anna-Elina Lehesjoki, Mikael Lindlöf, Ismo Söderling, Antti Uutela, Helena Kääriäinen

Abstract
The question of whether genetic carrier testing should be performed on children has been the subject of much debate. However, one important element has been lacking from this debate. There has been practically no knowledge of how those tested in childhood have experienced carrier testing. Twenty three subjects in families affected by Duchenne muscular dystrophy and 23 in families affected by haemophilia A, all of whom had been tested during childhood for carriership in the Department of Medical Genetics, University of Helsinki, from 1984 to 1988, participated in our study. We investigated long term psychosocial consequences of carrier testing in childhood. A questionnaire relating to sociodemographic background and life situation was used, together with assessment of health related quality of life (HRQOL) using the RAND 36 item Health Survey 1.0 (RAND). RAND results showed that the emotional, social, and physical well being of the young female subjects was not statistically different from those of control female subjects at a similar age. We also found no statistically significant differences in means in any RAND dimension (p<0.146) between carriers, non-carriers, and a group in which carrier status was uncertain. However, two out of seven carriers reported that they were worried and three that they were slightly worried about the test result. Four out of 22 young female subjects in the uncertain group reported being worried and 11 reported being slightly worried.

Keywords: carrier testing in childhood; health related quality of life; psychosocial consequences; RAND

When a child is diagnosed as suffering from a hereditary disease, its parents usually want to know about the carrier status of healthy sibs. It has been, and probably still is, common practice to test sibs for possible carriership. The British Working Party of the Clinical Genetics Society has suggested that the carrier status of children should not be determined solely in relation to possible future reproduction. This suggestion has been followed in Finland and, presumably, adopted in most western countries. However, justifications can be advanced for both testing and not testing children. Advantages include creating opportunities for children to adjust to their situations, fostering of openness within families, relief of parental uncertainty, and comprehensiveness of family testing. Disadvantages include possible harm to a child’s self-esteem, distortion of family perception of a child, and deprivation of choice in adulthood of deciding whether to be tested. No data have been available about how those tested in childhood have reacted to the experience.

There have been several studies of the psychosocial consequences of carrier testing of adult family members, and of population screening for carriers of recessive diseases, such as cystic fibrosis, Tay-Sachs disease, β thalassaemia, and sickle cell trait. No serious adverse effects have been found in the studies cited, but various degrees of anxiety have been found to be associated initially with detection of carriership. Anxiety mostly seems to decline with time. Some carriers have been found to have less positive feelings about themselves, or their current health, and less optimistic views about future health than non-carriers. In a study of experience of carrier testing for X linked disorders in adulthood, non-carriers were found to feel emotional relief, but carriers felt sadness and loss of reproductive expectations.

There have been very few studies of the psychosocial consequences of carrier testing or screening during adolescence. In two, carriers were initially found to experience anxiety, which declined with time. However, prolonged worry about carrier status and regret at having been tested have also been reported.

Only one report of the psychosocial consequences of genetic carrier testing in childhood has been published. It concerns retrospective evaluation of testing of carriers of balanced chromosomal rearrangements through interview of members of 10 nuclear families. Learning about carrier status had caused transient psychological disruption, accompanied by feelings of unjustified stigmatisation. The results of this study and of studies in which carrier testing was evaluated during adolescence suggest that testing causes no serious distress or clinically important levels of anxiety.

More information about the consequences of genetic testing in childhood is obviously needed. The aim of our study was to determine whether there had been any long term psychosocial consequences of carrier testing performed eight to 12 years previously in female...
children and teenagers in families with X linked recessive diseases (Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) and haemophilia A (HA) or B (HB)). The main variables studied were emotional well being, social and physical functioning, general health, marital status, and reproductive behaviour.

**Subjects and methods**

**DISEASES**

DMD and BMD are X linked recessive muscular dystrophies. DMD occurs in boys under 5 years of age and causes progressive muscle weakness, usually leading to the death of subjects in their 20s from respiratory complications. Age of onset of BMD is later and life spans are longer. Both progressive diseases are usually considered difficult and depressive for females.19

HA and HB are X linked recessive bleeding disorders. Affected subjects bruise easily and suffer joint and muscle haemorrhages, prolonged bleeding from wounds, and excessive, sometimes fatal, haemorrhages after trauma. Improvements in the treatment of haemophilia over the past 20 years have considerably changed the prognosis. Nevertheless, haemophilia remains a chronic, often serious, disease,14 and life long replacement therapy for the deficient coagulation factor is needed.

With X linked recessive inheritance, only males are affected but female relatives can be carriers. Any sons of symptom-free female carriers have a 50% chance of being affected. It is often possible to perform genetic tests on healthy female family members, even in childhood, to determinate carrier status. There are two basic methods of studying carriership, direct mutation testing and linkage studies. The former confirms or excludes carriership with certainty. The latter is associated with varying degrees of uncertainty.

**METHODS**

**Contacting families**

The parents of families were approached by mail by the doctor who had counselled them at the time of testing. They were asked to inform their daughters about the study and ask whether they would be willing to participate. The subjects tested (mostly adult at the time of our study) were therefore contacted only via their parents. A questionnaire with a reply paid return envelope was sent to daughters who consented, provided that they were at least 15 years old. If no reply had been received within six weeks, a reminder was sent. Letters and questionnaires were mailed and received back between October 1996 and February 1997. Families who did not reply were subsequently contacted by telephone.

**The questionnaire**

The questionnaire contained some 100 questions, mostly multiple choice, the rest open ended. The first part of the questionnaire consisted of items relating to sociodemographic background, life situation, and testing of health related quality of life (HRQOL) by means of the RAND 36 item Health Survey 1.0 (RAND).23 The multi-item RAND scale relates to eight aspects of quality of life: (1) physical functioning, (2) role limitations related to physical health, (3) role limitations related to emotional problems, (4) energy/fatigue, (5) emotional well being, (6) social functioning, (7) pain, and (8) general health. The scale has been translated into Finnish and adapted to the Finnish culture.23 Possible concern about the result of testing was evaluated by the question: “If you were a carrier or your test result was uncertain, are you worried about it?” The question had five possible answers (yes, slightly, cannot say, indifferent, no). The remainder of the questionnaire was intended to evaluate experiences relating to testing, and how test results were comprehended by the children tested. Results in this connection will be reported later.

**Statistical methods**

All RAND scores were transformed linearly into values ranging from 0 to 100, as suggested...
Higher values represented better physical, mental, or social functioning and well being.

Respondents were divided into six groups based on disease and carrier status: haemophilia carriers/non-carriers/those in whom test results had been uncertain, and muscular dystrophy carriers/non-carriers/those in whom test results had been uncertain. The subjective perception of carriership by the respondents was assessed by a question: “What was the result of genetic carrier testing?” There were eight possible answers: (1) I am a carrier (risk over 95%), (2) I am at very high risk of being a carrier (risk 90 to 94%), (3) I am at high risk of being a carrier (risk 60 to 89%), (4) I am at moderate risk of being a carrier (risk 20 to 59%), (5) I am at low risk of being a carrier (risk 5 to 19%), (6) I am not a carrier (risk under 5%), (7) the test result remained uncertain, (8) cannot say. The carrier group consisted of those who considered themselves to be carriers or at over 90% risk of being carriers. Non-carriers were those who, after having been tested, understood the risk of their being carriers to have been excluded or to be very low (under 5%). The uncertain group consisted of those who considered themselves to be carriers or at over 90% risk of being carriers. Non-carriers were those who, after having been tested, understood the risk of their being carriers to have been excluded or to be very low (under 5%).

Table 2  Results of telephone interview with seven mothers who did not respond to letter or questionnaire

<table>
<thead>
<tr>
<th>Why did the mothers not reply?</th>
<th>One mother said that she did not receive the questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two mothers did not like the questionnaire</td>
<td></td>
</tr>
<tr>
<td>One mother was angry about the questionnaire, because it brought back bad memories (her affected son had died)</td>
<td></td>
</tr>
<tr>
<td>One mother forgot to post the questionnaire</td>
<td></td>
</tr>
<tr>
<td>Two mothers said that there were many very personal questions, which made them reluctant to reply</td>
<td></td>
</tr>
</tbody>
</table>

What did the mothers think about carrier testing?

| Two mothers said that it might not be a good idea to test children |
| Four mothers thought carrier testing was a good idea |
| One mother was disappointed because carrier status remained unresolved |

| What was the test result? |
| 6/11 non-carrier |
| 4/11 carrier |
| 1/11 uncertain |

How many young female subjects tested in this group had not been told about their test result

| Of 11 young female subjects tested, 6 had not been told the results of their test |

All analyses were conducted using SPSS for Windows, version 7.0. Analysis of variance was...
Maternal level of education was used to describe the social backgrounds of subjects.

Data from Statistics Finland (from 1996).

Table 3: Sociodemographic descriptions of 37 respondents 18 to 29 years of age and of Finnish women of similar ages.

<table>
<thead>
<tr>
<th>Maternal level of education†</th>
<th>Duchenne muscular dystrophy (n=18)</th>
<th>Haemophilia A (n=19)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary school</strong></td>
<td>4 (22%)</td>
<td>6 (32%)</td>
<td>48*</td>
</tr>
<tr>
<td><strong>Vocational education</strong></td>
<td>4 (22%)</td>
<td>6 (32%)</td>
<td>43*</td>
</tr>
<tr>
<td><strong>Academic education</strong></td>
<td>1 (6%)</td>
<td>1 (5%)</td>
<td>6*</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>3 (16%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

Maternal level of education was used to describe the social backgrounds of subjects.

Table 4: Health related quality of life: the study group (haemophilia A (HA) and Duchenne muscular dystrophy (DMD) separately) versus control group.

<table>
<thead>
<tr>
<th>RAND dimension</th>
<th>Study group 95% CL*</th>
<th>Study group 95% CL*</th>
<th>Controls 95% CL*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMD (n=18)</td>
<td>HA (n=19)</td>
<td></td>
</tr>
<tr>
<td>Role functioning (emotional)</td>
<td>73.9–101.1</td>
<td>75.0–102.8</td>
<td>73.4–82.2</td>
</tr>
<tr>
<td>Emotional well being</td>
<td>72.1–84.3</td>
<td>73.6–87.2</td>
<td>70.2–74.5</td>
</tr>
<tr>
<td>Social functioning</td>
<td>86.3–98.4</td>
<td>85.7–97.1</td>
<td>83.0–87.9</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td>63.7–76.9</td>
<td>65.2–80.6</td>
<td>60.7–65.4</td>
</tr>
<tr>
<td>General health</td>
<td>72.8–87.2</td>
<td>72.6–88.5</td>
<td>73.8–78.1</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>92.6–101.5</td>
<td>96.4–100.8</td>
<td>93.6–96.9</td>
</tr>
<tr>
<td>Role functioning (physical)</td>
<td>81.2–102.1</td>
<td>71.6–102.3</td>
<td>84.3–91.3</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>82.1–94.5</td>
<td>80.2–96.7</td>
<td>80.0–85.5</td>
</tr>
</tbody>
</table>

*95% confidence interval for mean; no significant difference was found.

SOCIODEMOGRAPHIC CHARACTERISTICS OF RESPONDENTS

The mean age of young female respondents in the families with DMD was 21.7 years (SD 4.2 years) and in the families with HA it was also 21.7 years (SD 3.5 years). Sociodemographic characteristics are shown in table 3. The young female subjects in the families with HA had more often had only primary education and were more often cohabiting or married than the young female subjects in the families with DMD or the controls. Four out of seven carriers, 10/17 non-carriers, and 7/22 subjects in the uncertain group were married or cohabiting.

The nearest relative reported to be affected was a brother in the case of 30 respondents (65%). In the families affected by DMD, the nearest relative reported to be affected was a brother in the case of 18 respondents (78%) and in the families affected by HA 12 of the respondents (52%). There were usually also other affected subjects in the families. Four brothers with DMD had died.

Of the 46 young women tested, 11 had had at least one child or were pregnant. This was the case in 2/7 carriers, 6/17 non-carriers, and 3/22 of the uncertain group.

HEALTH RELATED QUALITY OF LIFE

Initially, all RAND scores for the young female subjects tested, who were 18 to 29 years old at the time of our study, in the case of both diseases were compared separately with scores for controls. There were no controls for RAND in the age group 15 to 17 years. When 95% confidence intervals for the means of all RAND scores were compared, the psychosocial well being of the subjects in our study was not statistically different from that of the controls (table 4). Similarly, when the means of all RAND scores were correlated with level of education, marital status, and occupation, none of the differences between the groups was statistically significant. The age groups 17 to 23 and 24 to 29 did not differ significantly from each other.

Secondly, means were compared for all RAND scores for all of the young female subjects tested, divided into carriers, non-carriers, and uncertain group members, in families with DMD and HA separately (table 5). None of the differences between the groups was statistically

Table 5: Health related quality of life: the study group (haemophilia A (HA) and Duchenne muscular dystrophy (DMD) separately) versus control group.
significant (p value greater than 0.146 for all groups using analysis of variance).

Thirdly, all RAND scores for the study population were calculated by marital status, by level of education, by testing age and age at which the test results were communicated, and by whether a brother was affected, for the two diseases separately. Results were analysed using the non-parametric Mann-Whitney test. No statistically significant differences between groups were found.

Finally, two out of seven carriers (29%) reported that they were worried and three (43%) that they were slightly worried about the test result. Four out of 22 young female subjects (18%) in the uncertain group reported being worried and 11 (50%) reported being slightly worried.

Discussion
This is the first study of late psychosocial consequences of genetic carrier testing for an X linked disorder in childhood. The young female subjects tested appeared to differ in respect to some sociodemographic characteristics from the controls. The controls were more often single and less often housewives than the young women tested. They had had more education than the young women in the families with HA. These differences could have affected RAND scores.

The young women who had been tested in the families with HA were more often married or cohabiting (63%) than those in the families with DMD (56%) or controls of the same age (45%). Being married or cohabiting was equally common in the group of carriers (4/7) and in the group of non-carriers (10/17), but less common in those in whom test results had been uncertain (7/22). In a previous study on the effect of Tay-Sachs heterozygosity on marital status in young adults 21 to 26 years of age, it was found that 32% of carriers were engaged or married, as opposed to 16% of non-carriers. These results would seem to indicate that identification as a carrier of a Mendelian disorder does not result in hesitation as regards marriage.

The RAND scores show that the young female subjects tested had at least as good emotional, social, and physical well being as the controls. Our study therefore shows that carrier testing resulted in no measurable distress to the subjects tested. However, it has been argued that such a finding can mean two things: either that the psychosocial well being of the participants was in fact very good, or that the result reflected defensive denial of the participants. Many subjects apparently live and cope well through such defensiveness, which becomes part of their normal lives.

No statistically significant differences in means between carriers, non-carriers, and members of the uncertain group existed in relation to any RAND score (p>0.146), but the groups may have been too small for significance to be demonstrable.

The RAND test has been widely used in various studies, for instance in evaluating HRQOL in a random population sample and in patients with different diseases. The advantage of such a generic battery of tests is the possibility it allows of comparing populations of interest with normal populations of similar ages. RAND is considered to be comprehensive, with sensitivities and validities better than those of many other generic test batteries (for example, the Quality Well-being Scale, the Rosser Index, or the Sickness Impact Profile) because it explores several dimensions in relation to quality of life, and there are more than two response options for each question. Although the RAND test is regarded as reliable for evaluating HRQOL, comprehensive interviewing of a group of the young female subjects tested would extend our study results.

There are three limitations to our study population. Firstly, the small number of young women studied limited the possibility of detecting differences between subgroups. Since the diseases concerned are rare, the study material could not be extended. Secondly,
telephone interviews with mothers who did not complete a questionnaire or pass one to their daughters showed that the families were selected, in that 6/11 daughters had not been told about the test result. Thirdly, a better control group would have been untested sisters or cousins of affected male subjects. Such a group could not be formed, because practically all such subjects in the entire country had been tested at the time.

The results of the study reported here show that the young female subjects tested had experienced good emotional, social, and physical well being in their lives. However, most of those who were carriers or members of the uncertain group reported being concerned about the results of testing. In our study population, no respondent reported severe symptoms, such as psychiatric illness, severe anxiety, or attempted suicide. In an evaluation of the consequences of identifying children as carriers of balanced chromosomal rearrangements conducted by interviewing the subjects tested at least 10 years afterwards, it was found that learning about carrier status had caused transient psychological disruption, but that after 10 years some subjects were indifferent to their carrier status, while others reported feelings and experiences of stigmatization. 17

There have been some studies relating to screening or carrier testing of recessive diseases during adolescence.15-16 It is difficult, and may even be impossible, to compare the results of our study with the results of the studies cited because screening or carrier testing was carried out in a completely different context. Our retrospective investigation showed that genetic carrier testing during childhood resulted in no measurable disturbance of quality of life in adulthood. The study population was, however, fairly small. Evaluation of a larger group through international collaboration might yield more meaningful results. Absence of evidence of adverse effects cannot be considered as a reason for proceeding with testing of children. If such tests are performed in young children, their privacy and freedom to choose for themselves are inevitably violated.

This study was supported by the Academy of Finland. We also wish to thank all the families and young female subjects who participated in this study.