PATERNAL ALCOHOL EXPOSURE AND TURNER SYNDROME

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Abstract — Aims: Turner syndrome (TS) is a sex chromosome aneuploidy that occurs as a result of a non-disjunctional error in meiosis I or anaphase lag; however, the aetiology of this disorder remains unknown. Anecdotal evidence suggests that paternal alcoholism may play an unidentified role in the aetiology of TS. Accordingly, the primary objective of this study was to determine the potential association between paternal alcohol exposure and TS. Methods: The questionnaire was designed to solicit information about the parents’ health and lifestyle habits occurring 1 year prior to and throughout the pregnancy of their daughter with TS. Alcohol dependence was assessed by the Brief Michigan Alcohol Screening Test (BMAST). The study population was solicited from the Turner’s Syndrome Society of Canada and included any parent(s) having a child with TS who was of any age. Two hundred and twelve families completed and returned the survey. Results: This provided a response rate of 86.5%. Six of the fathers (3.6%; n = 166) and six of the mothers (3.6%; n = 165) had scores of 5 or more on the BMAST (scores of 5+ are considered to be in the ‘alcoholic range’). This is considerably lower than the population norm of 9.5%. Conclusions: Our study has suggested there is no association between paternal or maternal alcohol consumption and TS.

INTRODUCTION

Turner syndrome (TS) is a genetic condition that affects 1 in 5000 female live births (Smith and Jones, 1988; Lippe, 1991). It occurs as a result of a loss or structural alteration of one of the X chromosomes during oogenesis or early embryonic development. Individuals with TS have a classic pattern of physical, cognitive and psychological characteristics that have life-long implications for their emotional well-being. Although these problems are widely variable, certain characteristics, such as significantly short stature and infertility, are more prevalent than others.

There are a number of physical features that characterize TS. These mainly include significantly short stature (mean height is 4’ 8”’) and gonadal dysgenesis. Some women with TS may have an unusual appearance due to skeletal abnormalities such as a short neck, shield chest, wide spaced nipples, numerous pigmented nevi, cubitus valgus, craniofacial abnormalities, nail abnormalities and scoliosis. There are also a number of associated medical problems including coarctation of the aorta, hypertension and renal abnormalities, such as horseshoe kidneys (Smith and Jones, 1988; Stevenson et al., 1993; Ogata and Matuso, 1995; Elsheikh et al., 1999, 2002; Nathwani et al., 2000; Landin-Wilhelmsen et al., 2001).

This sex chromosome aneuploidy occurs as a result of a non-disjunctional error in meiosis I or anaphase lag; however, the aetiology of this disorder remains unknown (Martinez-Pasarell et al., 1999). Between 60 and 80% of live born TS individuals have lost the paternally derived X chromosome (Hassold et al., 1985, 1988; Stevenson et al., 1993; Monroy et al., 2002). Moreover, 90–99.9% of XO conceptuses aborted and the XO karyotype occurs in 1 of 15 spontaneous abortions (Carr and Gideon, 1977; Warburton et al., 1980; Stevenson et al., 1993). In previous investigations, aetiological factors, which have been examined, but remain unresolved include: the association of a seasonal incidence of the disorder (Carothers et al., 1980; Videbech and Nielsen, 1984), birth order (Carothers et al., 1980) and the relationship between autoimmune disorders and the incidence of TS (Salmon and Ashworth, 1970). Furthermore, the roles of environmental or lifestyle factors, such as maternal or paternal alcohol and drug consumption, therapeutic medications, smoking and numerous other determinants of health, in the pathogenesis of TS, have not been systematically investigated or reported (Lippe, 1991).

In a recent qualitative analysis, one of the investigators (S.K.) interviewed 11 women with TS to determine how the experience of TS had affected their lives, and how they learned to cope with the disorder (Kagan-Krieger, 1998). Eight out of 11 women came from families where the fathers were described as ‘heavy drinkers’ or ‘alcoholics’. The sample in this preliminary study was too small to make any statements about the association of paternal alcohol consumption and the pathogenesis of TS. These findings did, however, warrant further investigation, because it is known that alcohol can affect spermatogenesis and sperm function (Cicero, 1994; Donnelly et al., 1999). Our hypothesis from this preliminary study was that paternal alcohol consumption might have a biological effect on the developing fetus. The association between maternal alcohol consumption during pregnancy and an increased incidence of birth defects, such as those associated with fetal alcohol syndrome, has been well documented (Coles, 1994; May and Gossage, 2001). However, the possibility that paternal alcohol consumption may also cause chromosomal defects in the fetus has received little attention in the literature (Abel, 1989; Cicero, 1994; Coles, 1994). There are three possible mechanisms to account for the effect of paternal alcohol consumption on the fetus: (1) alcohol consumption may directly affect the characteristics and properties of sperm by causing mutations in the sperm’s genetic material; (2) alcohol consumption may only leave a specific population of sperm to remain functionally intact; (3) alcohol consumption may influence the activity of...
ejaculated sperm by altering the chemical composition of semen (Cicero, 1994). Hence, the primary objective of this study was to determine the potential association between paternal alcohol exposure during fetal life and TS. To date, there has been no research that has provided this information.

SUBJECTS AND METHODS

Overview of the research design

This study employed a self-report survey methodology. This design has been shown to be useful in collecting sensitive data on substance misuse, since it minimizes personal contact with the participants (Trinkoff and Storr, 1997). The participants were mailed a health and lifestyle questionnaire, that took approximately 20 min to complete. Direct questions about how much a participant drinks may trigger denial and minimization of intake, especially in heavy drinkers (Sokol et al., 1985; Wallace et al., 1987). For example, the sensitivity of a screen for alcoholism fell from 95 to 32% when questions on the quantity and frequency of drinking were asked prior to the screening (Steinweg and Worth, 1993). As a result, studies that focus on generating data about such sensitive topics may collect inaccurate information, if the aim of the investigation relates directly or exclusively to soliciting data about the participants’ drinking habits. They may feel guilty and embarrassed, thereby covering up the reality of their lives (Trinkoff and Storr, 1997). Therefore, this investigation assumed a more indirect approach and used a general health and lifestyle survey to ensure that the participants were unaware that the primary purpose of this study was to determine patterns of paternal alcohol intake. Accordingly, the parents of children with TS were investigated to determine whether or not pre-determined lifestyle factors or health-related determinants, such as smoking, exercise, alcohol and drug use, and diet may be implicated in the aetiology of TS. Considering that the primary objective of this study was to determine the potential association between paternal alcohol exposure during fetal life and TS, this paper will report only the findings related to parental alcohol use and consumption. The remainder of the findings related to the other health and lifestyle factors will be reported in subsequent papers. Furthermore, although the focus of this study is on paternal alcohol exposure, in order to provide a complete and comprehensive perspective, we will report the data related to alcohol use we have collected on both mothers and fathers.

Subjects

The subjects were solicited from the Turner’s Syndrome Society of Canada. The Society is a non-profit organization developed to provide support and education to individuals with TS and their families. There are approximately 389 active members on their mailing list from across Canada, the USA and a few from Australia. Any mother or father of a child with TS of any age was eligible to be involved in this study. It was not necessary that the parents were cohabiting at the time they completed the questionnaire. Therefore, parents who were single, separated or divorced were also included. Finally, the participants needed to be able to understand and respond to the questions on the survey written in English or French, and were geared to a grade six reading level (Aday, 1996). A letter describing the study and requesting their voluntary participation was sent to all members. Ethical approval for this study was granted by both the Turner’s Syndrome Society of Canada and The Hospital for Sick Children in Toronto. Informed consent was provided by each participant.

The questionnaire

The primary outcome measure included in the questionnaire is an unrevised form of the Brief Michigan Alcohol Screening Test (BMAST). The BMAST was developed from the original version of the MAST, which consists of 25 direct questions about the participants’ drinking behaviour and any problems that may be associated with it (Hedlund and Vieweg, 1984). Some investigators believed that the 25 questions making up the MAST were excessive and that there was a need for a shortened version of the test (Pokorny et al., 1972). Accordingly, the BMAST was developed, which consists of 10 questions derived from the original MAST.

Pokorny et al. (1972) performed an investigation to determine if the BMAST would be as effective as the MAST in discriminating between alcoholics and non-alcoholics. Correlations between scores on the BMAST and MAST were high, ranging from 0.95 to 0.99. The investigators demonstrated that the two versions of the MAST discriminate well between alcoholics and non-alcoholics. In addition, they suggested that the 10 question BMAST is as good as the 25 question MAST and ‘is superior in situations where brevity is desirable’ (Pokorny et al., 1972, p. 345).

All BMAST items require a simple yes/no response. Individual items are assigned scores of 0, 1, 2 or 5 points, if answered in a significant direction and the BMAST (total score) is the sum of all individual response scores (Hedlund and Vieweg, 1984). The BMAST has a total score range of 0–29 points. A score of 5 or more represents a possibility of an alcohol-related problem including alcohol misuse. A score of 20 indicates a high probability of alcohol dependence (Selzer et al., 1975; Reynolds et al., 1992).

Originally, the MAST was developed by Selzer (1967, 1971) as a questionnaire to be individually administered by an interviewer. Many of the MAST items have also been used by other investigators in surveys of alcoholism (Hedlund and Vieweg, 1984). It has been used with many different subject groups and as an epidemiological tool in prevalence surveys of general community populations (Brady et al., 1982; Hedlund and Vieweg, 1984). Test reliability using internal consistency and retest methods for lifetime alcohol problems are well established and relatively high (alpha = 0.83–0.95) (Selzer et al., 1975; Zung, 1982). The validity has also been well documented in the literature (Selzer et al., 1975; Zung, 1982, 1984; Hedlund and Vieweg, 1984). The accuracy of the MAST in identifying diagnosed alcoholics is from 79 to 100% (Hedlund and Vieweg, 1984). For example, the validity coefficients reported by Selzer et al. (1975) for the MAST total scores and alcoholism versus control group membership were impressive (alpha = 0.79–0.90) (Hedlund and Vieweg, 1984).

Additional questions about the participants’ amount and frequency of drinking behaviour were also included in the questionnaire. We defined the quantity of alcohol consumed based on standard drinks. One standard drink (13.6 g ethanol) = 341 ml (12 oz) of beer of 5% ethanol, 142 ml of wine of 12% ethanol or 43 ml (1.5 ounces) of spirits of 40% ethanol.
In 1997, the Addiction Research Foundation, now a division of the Centre for Addiction and Mental Health, published low risk drinking guidelines (CCSA and CAMH, 1999). Men should drink no more than 14 standard drinks and women no more than nine standard drinks per week. The guidelines also recommend no more than two standard drinks per drinking occasion. Risky drinking is defined as drinking above these guidelines. Research has suggested that a spouse or partner may be a more reliable source of information about drinking problems, than the alcoholic (Morse and Swenson, 1975). Hence, each participant was requested to answer questions about their partner’s amount and frequency of alcohol consumption as a means of cross-checking the accuracy of the self-reported data collected in the survey.

All questions were designed to solicit information regarding the parents’ health and lifestyle habits, particularly alcohol consumption, 1 year prior to and throughout the pregnancy of their daughter with TS.

Individual questionnaires were developed for mothers and fathers. The questions are identical; however, they were reworded to be gender appropriate. The questionnaires were also translated into French, in order to accommodate the membership in Quebec, who spoke and understood only French (30% of the sample).

The survey was conducted between September 1999 and March 2000. Initially, the questionnaire was test-piloted on 15 parents randomly chosen from the membership of the Turner’s Syndrome Society. Minor revisions were made to the questionnaire subsequent to reviewing the pilot data. The pilot data were included in the final data pool. Follow-up enquiries were performed to ensure that there was a high response rate to the questionnaire (Dillman, 1978; Henry and Zivick, 1986; Hill et al., 1997). The survey development and mailing process highlighted by Dillman (1978) in the Mail and Telephone Surveys—The Total Design Method has resulted in response rates that are generally 70% and higher (Dillman, 1978; Abson and Gentemann, 1996). This method provides specific instructions on the mailing process and follow-up procedure that was implemented in this survey: an initial mailing, followed by a thank-you or reminder post card, a second reminder, a second mailing of the questionnaire and a follow-up telephone call to the non-responders.

Statistical analysis

Data were expressed as percentages, means and standard deviations. Differences between subgroup reports were compared using Student’s t-test for unpaired data. The incidence of problem drinking based on the BMAST among fathers of girls with TS was compared to the incidence of problem drinking from Canadian data published by Reynolds et al. (1992) using a chi-square test.

RESULTS

The survey was sent to 245 families, of which 212 completed or partially completed and returned the questionnaire. This provided an overall response rate of 86.5%. Typical of most surveys, not all questions were answered by all participants. Therefore, the sample size for those that answered the completed set of questions for the BMAST, frequency of drinking and the amount of alcohol consumption will be reported individually.

The mean age of the fathers at the time of conception of their daughter with TS was 32 years (range 16–50 years). The mean age of the mothers at the time of conception was 29 years (range 19–42 years). At the time the questionnaire was completed, the mean age of the fathers was 52 years (range 24–84 years), the mean age of the mothers was 50 years (range 19–88 years) and the mean age of the daughters was 21 years (range 1–54 years).

BMAST scores

Six of the fathers (3.6%; n = 166) and six of the mothers (3.6%; n = 165), had scores of 5 or more on the BMAST. Two of the fathers (1.2%; n = 166) and one mother (0.6%; n = 165) had scores greater than 20 on the BMAST suggesting severe and advanced alcohol-related problems (Fig. 1).

We compared the rate of paternal problem drinking based on the BMAST to the figures described by Reynolds et al. (1992) in the Hamilton–Wentworth Health Survey. The rate of problem drinking of 9.4% (11 100/121 600) was significantly higher than in the present study (3.6%; 6/166) (P = 0.02).

Frequency of drinking

Each parent was asked to report on how often they consumed drinks containing alcohol. Overall, 68 of the fathers (41%; n = 165) and 21 of the mothers (10.9%; n = 191) reported drinking more than two to three times a week. A subset of this group reported drinking four or more times a week [28 of the fathers (17.0%) and five (2.6%) of the mothers] (Fig. 2).
Amount of alcohol consumption

Each parent was asked to report on the number of standard drinks they consumed in a typical day. As shown in Figure 3, 23 of the fathers (12%; \( n = 179 \)) and 10 of the mothers (7.6%; \( n = 130 \)) reported drinking three or more drinks a day. Nine of the fathers (6.43%) reported having four drinks a day, three (2.14%) reported having six drinks per day, two (1.1%) reported having eight or more drinks per day. Two of the mothers (1.54%) reported having four or more drinks a day and one mother (0.77%) reported having five or more drinks a day (Fig. 3).

Validation of the frequency and amount of drinking

Each parent was asked to report on their partner’s amount and frequency of drinking. The fathers reported drinking on average two to three times a month and the mean number of drinks was 0.74 in a typical day. As shown in Figure 3, 23 of the fathers (12%; \( n = 179 \)) and 10 of the mothers (7.6%; \( n = 130 \)) reported drinking three or more drinks a day. Nine of the fathers (6.43%) reported having four drinks a day, three (2.14%) reported having six drinks per day, two (1.1%) reported having eight or more drinks per day. Two of the mothers (1.54%) reported having four or more drinks a day and one mother (0.77%) reported having five or more drinks a day (Fig. 3).

DISCUSSION

Our original study made a possible link between paternal alcohol use and TS likely. However, there was certainly selection bias in a small-scale qualitative study. It is biologically plausible that paternal alcohol consumption could lead to TS, due to the effect of alcohol consumption on chromosomes, sperm counts and sperm morphology (Donnelly et al., 1999). It is of potential interest that 60–80% of all cases of TS are due to a missing paternal X chromosome, lending more credibility to our hypothesis. Our study shows that fathers of patients with TS did not have higher rates of problem drinking than the general Canadian population. In fact it was lower. This may be explained by recall bias, as it is often difficult to remember actual alcohol consumption patterns several years prior to the survey. However, the BMAST is a screening test for lifetime alcohol problems. Our lower prevalence of alcohol problems, as compared to the general population, may indicate that respondents did not accurately answer the questions, due to possible guilt that their behaviour might have led to the development of TS in their daughters. However, the excellent concordance of responses from spouses makes this very unlikely. The BMAST is sensitive to patients with alcohol dependence, but may have missed heavy alcohol consumers (i.e. problem drinkers).

Our study is the largest ever survey of drinking behaviour in parents of people with TS. It is unlikely that alcohol consumption by parents leads to the development of TS. The search for the aetiology of this condition still remains elusive but seems to exclude alcohol as a possible factor.

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