Autistic-like behaviour profile and psychiatric morbidity in Fragile X Syndrome
A prospective ten-year follow-up study

Abstract In subjects with Fragile X Syndrome (FXS), the mutation of Fragile X Mental Retardation Type 1 (FMR1) gene at Xq27.3 predisposes to Mental Retardation (MR), autistic-like behaviour and to a variety of psychiatric syndromes. However, the longitudinal course of autistic-like behaviour profile and psychiatric morbidity is untested. In this study, we followed up people with FXS for 10 years to establish the stability of their autistic-like behaviour profile and psychiatric morbidity. The autistic-like behaviour profile was assessed using Brief Disability Assessment Schedule (B-DAS) and relevant items from Handicaps, Behaviour and Skills (HBS) Schedule. The psychiatric morbidity was assessed using data from the case notes, Mini Psychiatric Assessment Schedule for Adults with Developmental Disability (Mini PAS-ADD) and clinical interview. Our findings suggest that the autistic-like behaviour pattern is a stable phenotypic feature of FXS, but for increase in resistance to change over time. There is a ten-fold increase in the prevalence of psychiatric morbidity in FXS compared to the general population, which does not increase significantly over time.

Key words Fragile X Syndrome – autistic-like behaviour – autism – follow-up – psychiatric morbidity – prevalence

Introduction

Fragile X Syndrome (FXS) is the commonest inherited cause of Mental Retardation (MR) occurring at a rate of 1 in 4000–6045 male births (Turner et al. 1996; De Vries et al. 1997). It is caused by a mutation in the Fragile X Mental Retardation Type 1 (FMR1) gene at Xq27.3 on the X chromosome. A significant minority of males with fragile X mutation have autism (Margolis et al. 1999); however, the autistic-like behavioural features are seen in almost all patients with FXS (Margolis et al. 1999; Hagerman et al. 1986). None of the follow-up studies so far (Hodapp et al. 1990; Wiegars et al. 1992; Dykens et al. 1996; Bailey et al. 1998; Brown et al. 1992; Musumeci et al. 1991; Einfeld et al. 1999) have looked at the longitudinal course of the autistic-like behaviour profile. The psychiatric morbidity among subjects with FXS and its longitudinal course have also not been systematically studied. Our study aims to establish whether an autistic-like behaviour profile and psychiatric morbidity changes over a 10-year follow-up period among people with FXS. We included both children and adults and used diagnostic instruments.
Methods

Study population

This population-based prospective cohort study was carried out between 1986 and 2000. The North-East Essex ethics committee approved the study protocol. The initial cohort of people with Fragile X Syndrome (5 years and over) were recruited between 1986 and 1989 from an epidemiologically derived sample of people with MR identified through health, social and educational services and living in the district of North-East Essex (N = 1371). Informed consent was sought from all the people identified. Where this was not possible due to lack of capacity, assent from the principal carer was obtained. Two hundred and ten people refused consent to participate in this study.

Sixty-one unselected subjects with MR (39 males) had chromosomal analysis for FXS. This unselected procedure proved inefficient as it yielded only one person positive for FXS. Hence, those with an established aetiological diagnosis for their MR (e.g. Down's Syndrome, cerebral palsy, tuberous sclerosis, phenylketonuria) were excluded (N = 361). Clinical and anthropometric screening criteria (based on orchidometry, head circumference and ear length measurements) were applied to the remaining sample (N = 739) to select subjects for cytogenetic testing (Sabaratnam et al. 1994). There were 64 people meeting the selection criteria who underwent the cytogenetic testing. The cytogenetic confirmation of the sample was done at the Cytogenetics Unit, Essex county hospital. This test led to the identification of 25 people with FXS [mean (SD) age – 37.6 (22.5) years, range: 6–76 years, 24 males]. One subject died before the initial assessment and another withdrew consent at this stage. The remaining 23 people [mean (SD) age – 37.5 (22.2) years, range: 6–76 years, 22 male], were individually assessed by MS in 1989. The sample selection procedure is given in Fig. 1.

DNA testing

In 1989, the structure of the DNA could not be analysed as DNA testing was not introduced until 1991. Thirteen of the consenting and surviving individuals were studied again in 1996 to analyse their DNA structure. The DNA tests were carried out at the Kennedy Galton Centre in North-West London. Molecular evaluation of the FMR1 gene was performed by Southern Blot analysis using OX1.9 FMR1 Genomic probe. Double digest with Eag1 (New England Biolabs), a methylation sensitive endonuclease and EcoR1 (Gibco) permitted examination of both sizes of the CGG trinucleotide repeat and methylation status of the CpG island in the 5’ untranslated region of the gene.

In 2000, four of the initial cohort had died and the only female subject’s mother withdrew her consent for the follow-up assessment. Hence, only 18 subjects [mean (SD) age – 46.1 (18.8) years, range: 21–76, all males] were followed up (Fig. 1). Psychiatric diagnoses were established by looking through the case notes and clinical assessment on both the occasions. A carer screening instrument mini Psychiatric Assessment Schedule for Adults with Developmental Disability (not yet introduced in 1989) was also used during the tenth year follow-up.

Materials

Diagnostic and Statistical Manual (DSM-IIIR) (American Psychiatric Association 1987) was used to diagnose autistic disorder. The participant’s place of living, history of epilepsy and history of physical illnesses were noted.