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ORIGINAL PAPER

Triple X syndrome: characteristics of 42 Italian girls and parental emotional response to prenatal diagnosis

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Abstract We report clinical and behavioural evaluation data in 42 Italian girls with triple X syndrome whose diagnosis was made prenatally between 1998 and 2006 in three Italian centres. At initial evaluation, reproductive and medical histories were collected. Clinical assessment of the child was performed by a clinical geneticist and included a detailed personal history, physical evaluation and auxological measurements. To analyse how parents coped with specific events in the prenatal and postnatal periods, we conducted an interview that included 35 specific questions designed to elicit retrospective judgements on prenatal communication, present and future worries, needs and expectations. In a subset of probands, we also administered the formal Italian Temperament Questionnaire assessment test that investigates adaptation, general environment and socialisation. This test also assesses the emotional component of temperament. Clinical results in the affected children are similar to those previously reported with evidence of increased growth in the pre-puberal age and an average incidence of congenital malformation and health needs. Median age for the time first words were pronounced was 12 months, showing a slight delay in language skills, which tended to improve by the time they reached school age. Parental responses to the interview demonstrated residual anxiety but with a satisfactory adaptation to and a positive recall of the prenatal counselling session. Parental adaptation of the 47,XXX girls require indeed a proper educational support. This support seems to be available in Italy. An integrated approach to prenatal counselling is the best way to manage the anxiety and falsely imagined consequences that parents feel after being told that their foetus bears such a genetic abnormality.

Keywords 47,XXX · Triple X syndrome · Prenatal diagnosis · Genetic counselling · Parental adaptation

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Introduction

Nearly 50 years ago, the first report of a 47,XXX karyotype in a woman with secondary amenorrhea [10] initiated an

often conflicting discussion about the features of the "triple X syndrome" that only in the last two decades have a number of unbiased follow-up studies helped to define less ambiguously [2–4, 12, 14, 16, 19, 20].

47,XXX karyotype is present in about 1/1000 female births and is usually diagnosed incidentally, mostly at prenatal diagnosis. The clinical features are subtle and variable and include tall stature, short head circumference, an increased risk for speech delay, mild learning disabilities and poor motor coordination. Behavioural problems have been reported but are not fully confirmed. The vast majority of 47,XXX women are unaware of their abnormal karyotype.

Prenatal triple X diagnosis, due to its reduced clinical consequences, requires complex and challenging genetic counselling whose outcomes have not yet been fully documented. In fact, the discovery of such an anomaly during pregnancy always involves a great dilemma for the prospective parents who need to understand the clinical consequences and must then try to imagine the impact of an unexpected genetic condition on the quality of life of and their relation to their daughter [6, 13]. The lack of any direct experience in nearly all couples increases the anxiety arising from the diagnosis, and such unresolved anxiety could lead to an unwarranted termination of the pregnancy or might adversely alter their psychological relationship to their child.

The purpose of our study was to gather clinical data from the children and then to analyse the short and long-term psychological outcomes, obtained by both interviews and a well-defined questionnaire, of this prenatal diagnosis on parents of a large Italian cohort of 47,XXX girls.

Patients and methods

From January 1998 to January 2006, 67 Italian couples were referred to the major Maternity Units in Milan (n=34), Turin (n=24) and Genoa (n=9) for genetic counselling after the prenatal diagnosis of 47,XXX in the first or second trimester of pregnancy. All couples received a non-disclosing telephone call offering genetic counselling within 24 h of the diagnosis. In all cases, a foetal ultrasound examination was performed, and major congenital anomalies were excluded. Eight couples elected to terminate the pregnancy (Milano, n=6; Torino, n=1; Genova, n=1).

Starting in 2004, all couples who decided to continue the pregnancy were contacted by letter and by phone and invited to participate in a long-term survey that included clinical assessments of the child and a parental interview. Among these, 42 of 49 accepted and formed the basis for our study. The socio-economical status of our cohort was heterogeneous and was similar to that in the Italian population at large.

Reproductive and medical histories were collected. A clinical assessment of the child was performed by a clinical geneticist and included a detailed personal history, physical evaluation and auxological measurements. With the parents' consent, pictures of the children were taken to document dysmorphisms and familial traits. Information about the child's motor, behavioural and cognitive skills was also collected.

The parents' interviews were carried out by a clinical geneticist together with a clinical psychologist and included 35 questions aimed at evaluating how couples coped with specific circumstances of the prenatal and postnatal periods. Special attention was given to a retrospective judgement of prenatal communication, present and future worries and needs and expectations (Table 2).

In a subset of 23 patients evaluated in 2006 and 2007, we also used the "QUIT" questionnaire [1] administered to parents of girls in order to describe their child's temperament. The age range of patients was 12 months–6 years. This test provides an assessment of six factors concerning adaptation, three investigating general environment (motor activity, attention and inhibition to novelty) and three dealing with socialisation (social orientation, positive emotionality and negative emotionality). The test also assesses the emotional component of temperament highlighting four profiles (i.e., emotional, calm, difficult or normal). QUIT is currently the only standardised measure of temperament available in Italian. The questionnaire was administered to the mothers enrolled in the study. The mothers were asked to observe their children at home for a week and then to respond to questions about behaviour with other children, modes of play and reaction to novelty. All responses were expressed on a five-point Likert scale.

In late 2008, we carried out a telephone follow-up of 14 out of 42 families focused on collecting auxological measurements, state of health and school performance.

Clinical qualitative traits and interview data were evaluated by descriptive analysis. QUIT test data were compared to those derived from an age-matched Italian population.

Results

Medical history and clinical evaluation

Thirty-nine couples conceived naturally, while three pregnancies resulted from in vitro fertilisation. Prenatal diagnosis was requested for advanced maternal age (study mean, 37 years) or maternal anxiety; foetal ultrasound examination was normal in all cases.

Amniocentesis was the selected diagnostic procedure in 32 pregnancies, chorionic villous sampling in 10. With the

exception of the karyotype result, the pregnancies were uneventful in all cases. Foetal age at delivery, measures at birth, timing of motor and language development are summarised in Table 1 together with the description of congenital anomalies detected In our cohort.

Thirty-two children were reported as healthy, ten presented with recurrent diseases including bronchitis (n=5), dermatitis (n=2), otitis (n=1), cystitis (n=1) and bronchospasm (n=1). One child exhibited milk intolerance, and two had episodes of seizures with fever with normal neurological examination. No medications were taken on a regular basis.

The girls' height, weight and BMI were normal according to centile of Italian population [5].

Auxological evaluation confirmed a head circumference (HC) below average in the majority of children. There was no clinical indication to perform magnetic resonance. Comparing children with parents, the girls' HC was below the parental range in 29/42 cases. Children's heights were in the normal range for age and were concordant with parents' heights in 21/42 of children, below parental range in 14/42 and above parental range in 7/42.

At first evaluation and at follow-up, no relevant diseases were referred. Two girls underwent surgical interventions (one for inter-atrial defect and one for genus valgus). With respect to language skills, the mean age at first words was above average. Girls were a little late starting to crawl and taking their first steps but with a wide variation among individuals. They typically crawled at about 10 months (range, 5–20 months) and took their first steps around 14 months, but the range was 9 to 24 months. Despite an initial delay by school age, most of the girls performed normally in sports. All girls were reported to have a good primary school performance, but three of them were said to be lazy and needed to be encouraged and supported. Our protocol did not include QI evaluation according to the main goal of our study. All girls were normal in appearance. No dysmorphism was noted. Frequent facial features included oval face, epicanthus, mild hypertelorism, (mean value of interpupillary distance at 3 years for triple X girls with the same age was 52–53 mm with mean value for normal population at 46–50 mm) broad and slightly depressed nasal bridge (Fig. 1). These features were described by Nielsen [15] who demonstrated that girls with 47,XXX karyotype have significantly greater interpupillary distance, with a mean difference of 2.8 mm than the remaining children.

Table 1 Median and range of foetal age at delivery, measures at birth and timing of language and motor development of probands

	Min.–Max.	Median
Foetal age at delivery (weeks)	35–42	40
Birth weight (g)	1950–4200	3080
Length at birth (cm)	43–53	49
Head circumference at birth (cm)	32–37	33
Age at first words (months)	8–36	12
Age first walked (months)	9–24	14
Age at evaluation (years)	1–6	3
Congenital anomalies in six girls		Isolated ASD
		ASD + club feet
		Thyroid agenesis
		Lymphangioma
		Preauricolar tag
		Hyp dysplasia

Auxological parameters according to Gagliardi et al. [7]

ASD atrial septum defect

The parents' interview

Table 2 summarises questions included in the interview and answers of parents. The majority of interviewed couples considered the prenatal diagnostic test to have been very useful. In two cases only was it judged not helpful or useless. The first impact of the karyotype result in most cases was alarming, inducing states of uncertainty (9 cases), worry (15 cases) and trauma (15 cases).

Counselling by a medical geneticist allowed couples to regain a more favourable outlook.

In 15 cases of 42, worry returned to normal levels.

Most parents responded positively about the adequacy of information and support received. At the time of the follow-up interview, most parents clearly remembered what clinical information they had initially been given. In the parents' experience, their perception of their daughter was not particularly different from that of her siblings and of same-aged children; it should be noted that in the two cases in which the parents' perceptions of their affected children differed from their reaction to other children of a similar age, the affected girls also presented with other health problems.

The girls did not differ from same-aged peers in communication skills both with family members and strangers (17 cases of 37). The ability to participate in play activity was present in all cases except one.

For most parents, their daughter's future was either not worrying or was the cause of only slight concern (10 cases), while some doubts and fears remained in a few couples. Overall, among the couples interviewed, we noted a strong, special interest in future developments in genetic research related to triple X associated features.

QUIT test

As described before, we administered QUIT tests to parents of 23 girls aged 12 months to 6 years. This subgroup was

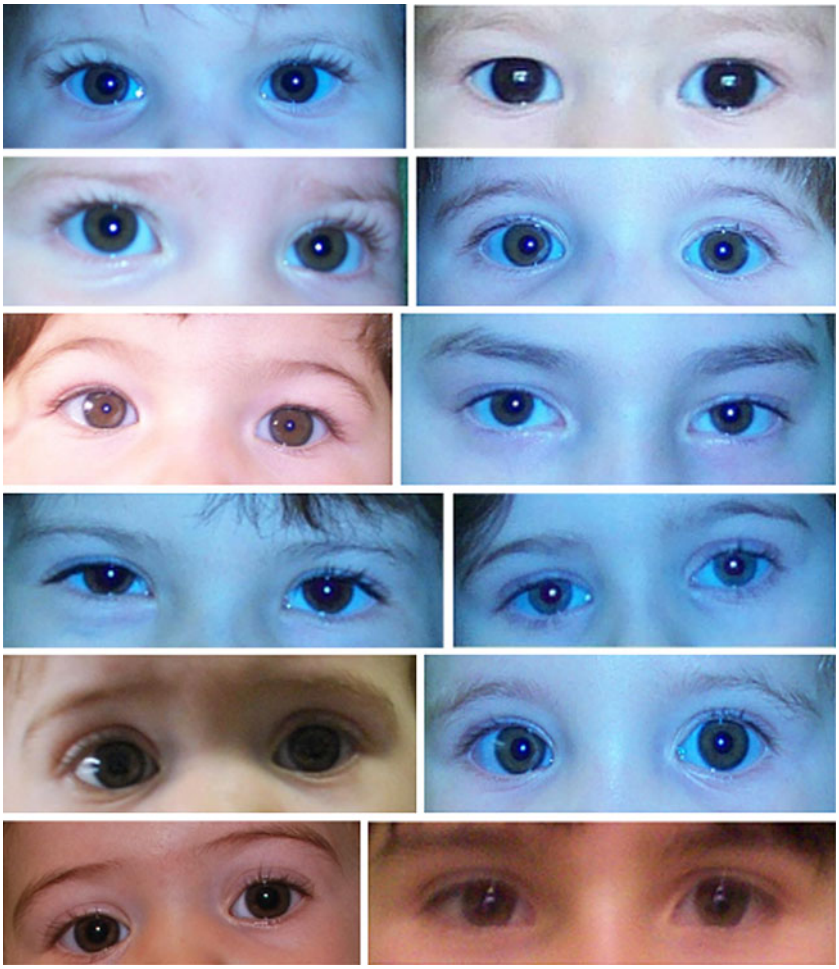

Fig. 1 Examples of orbital region of triple X probands showing mild hypertelorism, broad and slightly depressed nasal bridge

made of unselected cases. Three main areas were investigated: a) adaptation to environment; b) adjustment to the social environment; and c) emotional component of temperament.

Results are summarised in Table 3.

The theoretical reference frame considered for our observations led us to evaluate temperament as adaptive or maladaptive depending on the compliance with the

Table 2 Questions and answers of probands' parents at interview

Questions	Not at all	Not very much	Yes	Very much	Number
A) Do you think that prenatal diagnosis was useful in your case?	1	1	33	7	42
B1) Were you worried at karyotype communication?	1	2	24	15	42
B2) Were you worried after genetic counselling?	15	12	13	2	42
C1) Do you think that provided information was adequate?	0	3	28	11	42
C2) Do you think that genetic counselling supported you psychologically?	0	3	29	9	41
C3) Do you remember information received in genetic counselling?	2	1	31	8	42
D1) Do you perceive differences between your daughter and children of her age?	20	8	6	0	34
D2) Do you perceive differences between your daughter and her siblings?	8	13	6	0	27
E1) Does your daughter communicate with relatives?	0	3	28	2	36
E2) Does your daughter communicate with strangers?	0	11	25	1	37
E3) Does your daughter participate in play activity with other children?	1	6	27	2	37
F1) Are you interested in future updates regarding triple X karyotype?	1	3	27	11	42
F2) Are you worried about the future of your daughter?	18	10	12	0	40

Table 3 Results of QUIT test

Investigated area	Functional adaptation	Global functional adaptation	Global functional adaptation with exceptions	Adaptation potentially at risk	Normal	Difficult	Calm
Adaptation to environment	15	6[a]	1[b]	1[c]			
Adjustment to the social environment	10	6[d]	4[e]	2[f]			
Emotional component of temperament					21	1[g]	1[h]

[a] Except for "inhibition to novelty" that is above average (within 2SD)

[b] Except for attention (within 2SD)

[c] "Attention " below the average and "inhibition to novelty" above the average (within 2SD)

[d] Except for the emotional dimension (4 negative emotionality higher than the average, 1 positive emotionality below the average) (within 2SD)

[e] Except for "social orientation" below average (within 2SD)

[f] "Social orientation" and "positive emotionality" below the average (within 2SD)

[g] Average "negative emotionality" higher than "positive emotionality" (within 2SD)

[h] Low score in both positive and negative emotionality (within 2SD)

environment. The success or failure of an adaptation is not related to the individual but to the particular 'interface' between environmental demands and the resources that the individual has to adapt to that environment.

Discussion

To our knowledge, this is the first study that tries to evaluate the clinical features of a triple X cohort together with measures of the psychological impact of the prenatal diagnosis on their parents.

Our auxology data are in agreement with those previously reported. We observed HC's somewhat smaller than expected from parents' one. Yet the girls' heights were in the normal range and concordant with parental heights thus confirming that increased height mainly comes from mid-childhood and pubertal growth spurt. [17]. Dysmorphological evaluation confirmed some previously described features [15]. As documented in Fig. 1, some of our probands shared some facial features, particularly in the shape of the face and the ocular region. These features did not correspond to familial traits, and we believe they might represent a mild expression of a specific phenotype. A previous study of cephalometric analysis on four 47, XXX girls showed reduced linear measurements and suggested a retarding effect of an extra X chromosome on craniofacial growth [10]. In our sample, congenital anomalies were not significantly more frequent than in the general paediatric population. We did not observe an increased prevalence of genitourinary malformations or facial malformations as previously reported [9, 11, 21]. Medical needs in our sample were comparable with those of the general population.

As revealed by their parents' description, girls of our cohort do not present significant differences in physical development compared with their siblings and with other children of the same age. These results offer a positive profile of girls with 47,XXX karyotype in this period of life compared with previous reports of development in adolescence and early adulthood [8, 20].

Interview with the parents

During the interview, the majority of parents reported that the first communication of the karyotype was traumatic, alarming and inadequate. This might reflect the poor preparation of parents at the pre-test counselling session and inadequacy of the communication process at post-test counselling and might also be one explanation of the high incidence of termination, at least in Milano centre. It has been repeatedly suggested that women undergoing prenatal diagnosis of chromosomal anomalies need to receive more extensive information about chromosomal anomalies related to mild clinical consequences and to learn how to distinguish them from the more disabling ones. We have implemented our program with three initiatives to increase the positive adjustment of couples involved in prenatal diagnosis of triple X: 1) a more detailed counselling before prenatal diagnosis concerning minor chromosomal abnormalities 2) an adjustment of the mode and content of the first communication of an abnormal karyotype and 3) appropriate training of the staff involved in the communication process. The subsequent counselling conducted

by a geneticist had been clarifying and reassuring in most cases. Many couples have, for instance, welcomed suggestions about being careful of their own attitudes when disclosing the diagnosis to other family members, doctors, teachers and to their own children once they have grown.

We were able to document that if mothers could go back in time, they would undergo the same prenatal test because they recognised the value of prenatal diagnosis both for the exclusion of chromosomal abnormalities associated with more serious phenotypes and for the acquisition of knowledge in general.

The results of the questionnaire confirmed that birth of the child reassured the parents but that some concerns remained and were mainly focused on areas in which the literature has given ambiguous results. In this regard, we underline the tendency of couples to seek answers and information from unproven and unverified sources, with possible consequent unjustified anxiety and development of prejudices that are difficult to eradicate. Many parents have felt the need to further consult specialists. For this reason, at present, we offer parents the opportunity, after the birth of the child, to meet and talk with the individuals who were involved in the prenatal counselling session so as to deal with their concerns and help them to manage their anxiety.

QUIT test

Previous studies on teenage and adult subjects with triple X showed a wide variability in behavioural problems [2, 8, 18].

The assessment of the temperament in our paediatric cohort showed a normal functional adaptation in most girls. With respect to the factor “inhibition to novelty” (in particular emotional responses to strangers), the author of the QUIT test warns about the undeserved association between shyness and social anxiety, considering it a bias of western countries' cultural models that tend to penalise people who are reserved, unfriendly and very cautious in relating to another. In girls described as ‘shy’ that resulted in a QUIT test result with a high level of “inhibition to novelty”, we captured in most cases a cautious interpersonal approach with observation/selection of the other, rather than fear, social inhibition and consequent avoidance; of course, the sample small size must be taken into account (only 6 cases of 23). A diminished level of attention was present only in two cases (one of which was coupled with inhibition to novelty and other medical problems) and is within 2 SD: our sample size does not permit us to draw any more definite conclusions.

Regarding the adjustment to the social environment, we found in four girls a negative emotionality higher than the average, and in two girls a positive emotionality lower than average. In nearly the entire remaining cohort, the temperament is normal. This suggests that in our population, the higher negative emotions expressed in some cases are mostly balanced by an appropriate level of positive emotionality. This may not be true in older children and may therefore explain the difference with previous observations concerning adolescent and adult period [16]. More studies with additional tests on non-selected large cohorts are needed to evaluate girls' temperaments at different ages.

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Conflict of interest Authors declare no conflict of interest or any financial relationship with the organisation that hosted the research.

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