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Intestinal Atresia, Encephalocele, and Cardiac Malformations in Infants with 47,XXX: Expansion of the Phenotypic Spectrum and a Review of the Literature

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Established Facts

- Various types of malformations have been reported in 47,XXX females, of which urinary tract anomalies, in particular renal anomalies, are the most commonly reported defects. There have only been sporadic reports on gastrointestinal anomalies in females with 47,XXX and there has been only one previous report of an associated encephalocele.

Novel Insights

- We conclude that the prenatal identification of a 47,XXX karyotype is an indication for detailed fetal ultrasonography of multiple organ systems.

Key Words
Triple-X syndrome · Pancreas, annular · Atresia, duodenal · Encephalocele · Ventricular septal defect

Abstract
Identification of the 47,XXX karyotype often occurs adventitiously during prenatal fetal karyotyping in cases of advanced maternal age. Although most females with 47,XXX appear healthy at birth, various types of congenital malformations have been reported, of which urinary tract anomalies are the most frequent. We report on 2 newborns with 47,XXX and congenital cardiac defects, one of whom had duodenal atresia and the other an occipital encephalocele. This expands the spectrum of malformations reported in association with the triple-X syndrome. We also present a review of the literature on non-urinary tract malformations in females with 47,XXX. We conclude that prenatal identification of the 47,XXX karyotype is an indication for detailed fetal ultrasonography which should include examination of multiple or-

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gan systems. Such prenatal screening for possible associated congenital malformations should help to ensure optimal perinatal clinical management of 47,XXX cases.

Introduction

Sex chromosome aneuploidies are four times more frequent than autosomal aneuploidies, and the triple-X syndrome (karyotype 47,XXX) is the most frequent sex chromosome aneuploidy in live-born females (about 1 in 1,000) [1, 2]. Identification of this syndrome often occurs adventitiously during prenatal fetal karyotyping in cases of advanced maternal age [2, 3]. Various types of malformations have been reported in 47,XXX females, of which urinary tract anomalies, in particular renal anomalies, are the most commonly reported defects [2]. Postnatal ultrasonographic examination of the pelvis and abdomen in all females with 47,XXX has thus been proposed [4].

We report on 2 newborns presenting with the 47,XXX karyotype and various congenital malformations. Both infants had cardiac defects; one infant also had duodenal atresia due to an annular pancreas, and the other an occipital encephalocele. We review the literature on non-urinary tract anomalies in females with 47,XXX. Our report expands the spectrum of associated malformations reported for this karyotype.

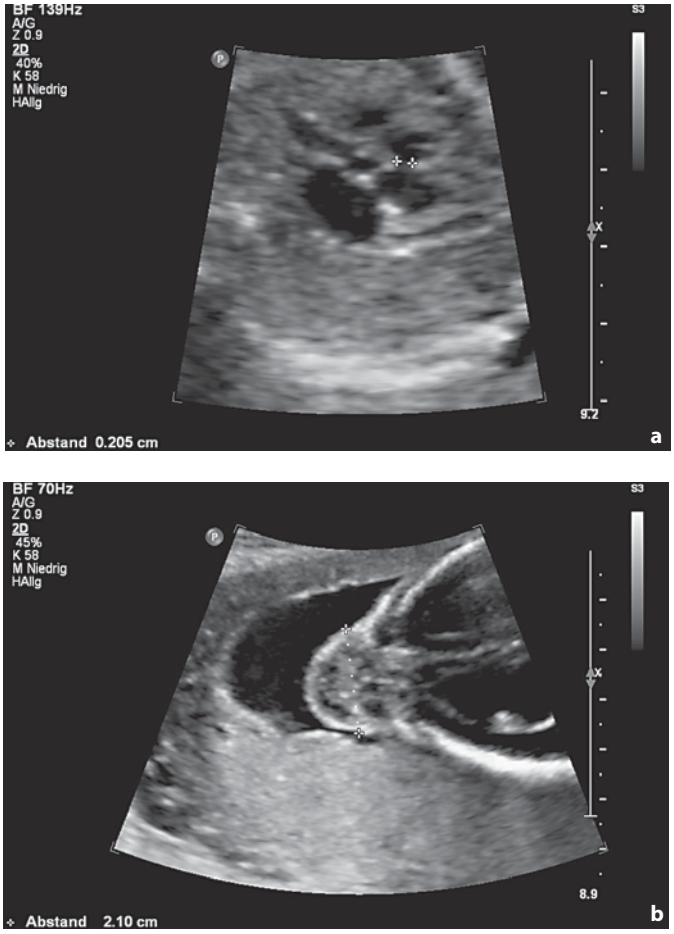

Fig. 1. Left ventricular outflow tract demonstrating the perimembranous ventricular septal defect (calipers; **a**) and the posterior encephalocele (calipers; **b**) at 20 weeks of gestation.

Case Reports

Case 1

Amniocentesis was carried out in the first gestation of a 37-year-old healthy woman on the grounds of advanced maternal age. This revealed that the fetus had a 47,XXX karyotype. The karyotype of the mother was normal and there was no family history of congenital anomalies. Ultrasound scans of the fetus were performed during the 29th week of gestation due to the presence of a severe polyhydramnion. These showed a 'double bubble' phenomenon in the fetus indicative of duodenal atresia. Amniodrainage was performed which caused premature rupture of the membranes and induction of premature labor at 31+2 weeks of gestation. A female infant was born by spontaneous vaginal delivery with a birth weight of 1,730 g. The Apgar scores at 1, 5, and 10 min were 8, 9, and 10. No dysmorphic features were evident at birth and clinical examination was normal. An abdominal X-ray taken at 2 h of age confirmed a 'double bubble' appearance. A laparotomy was performed when the infant was 5 days old, and duodenal atresia without malrotation due to an annular pancreas was found. Duodeno-duodenostomy was performed, and a small intestinal biopsy was taken to exclude aganglionosis. This biopsy was normal. Postoperative recovery was complicated by an anastomotic leak which was treated conservatively. Pre-discharge control echocardiography showed a small ventricular septal defect (VSD) and a patent ductus arteriosus. Elective catheter closure of the patent ductus arteriosus was planned, and the infant was discharged from hospital at the age of 2 months.

Case 2

A routine ultrasound scan performed in the 20th week of gestation of a healthy 31-year-old gravida 2, para 1 woman revealed that the fetus had a VSD (fig. 1a) and a large occipital mass (fig. 1b). Amniocentesis was performed which showed that the fetus had a 47,XXX karyotype. The karyotype of the mother was normal and the family history was unremarkable. The pregnancy proceeded without further incident. The infant with a birth weight of 3,380 g was delivered at 37 weeks of gestation by uncomplicated elective cesarean section. The Apgar scores at 1, 5, and 10 min were 8, 9, and 10. An occipital skin-covered encephalocele with a diameter of 2.5 × 5 cm was present, but no other dysmorphic features were observed. Cranial ultrasonography showed that the occipital horns of the lateral ventricles were massively dilated.

Table 1. Non-genitourinary anomalies in individuals with 47,XXX (including the present cases)

Reference	Patients, n	Gastrointestinal, cardiac, brain, and other anomalies	Additional genitourinary anomalies
Barr et al. [3], 1969	2	ASD[1]	n.a.
	1	Pulmonary artery stenosis[1]	n.a.
	1	Hydrocephalus[1]	n.a.
Sanchez Cascos [8], 1972	1	ASD[1]	n.a.
Robinson et al. [9], 1979	2	CHD (undetermined)[1]	n.i.
Hood et al. [6], 1990	1	Laryngeal atresia[1]	RA (unilateral)[1], OA/D[1], hydrometrocolpos[1], vaginal atresia[1]
Lin et al. [10], 1993	1	ASD[1]	CE[1], RA (unilateral)[1], OA (unilateral)[1], bifid uterus[1], rectoperineal fistula[1]
De Veciana et al. [14], 1994	1	Omphalocele[2]	RA (unilateral)[1]
Hoang et al. [15], 1999	1	ARM[1], EA[1], absent gallbladder[1]	OA/D[1], uterine hypoplasia[1], dysplastic horseshoe kidney[1]
Ehara and Eda [18], 2001	1	Schizencephaly[1]	n.a.
Haverty et al. [4], 2004	1	VSD[1], CPO[1], ARM[1], FD[1], nail aplasia/hypoplasia[1],	Hydroureter[2], dysplastic kidneys[2], duplicated vagina[1]
	1	OE[2], CHD[2] (undetermined)	multicystic kidneys[2]
	1	Omphalocele[2]	n.a.
Trautner et al. [16], 2004	1	Jejunal atresia[2]	n.a.
Kurtoglu et al. [11], 2004	1	ASD[1], aortic coarctation[1], craniosynostosis[1]	n.a.
Roth et al. [12], 2006	1	ASD[1], misalignment of pulmonary vessels with alveolar capillary dysplasia[1]	n.a.
Roubertie et al. [13], 2006	1	FD[1], mild pulmonary valve stenosis[1], hip dysplasia[1]	n.a.
Rolle et al. [17], 2007	1	DA[2]	n.a.
Jagadeesh et al. [19], 2008	1	CL/P[2]	n.a.
	1[3]	CL/P (bilateral), FD, sacral meningomyelocele, camptodactyly	VUR Grade III (unilateral)
Present case 1	1	VSD[1], PDA[1], DA due to annular pancreas[2]	n.a.
Present case 2	1	VSD[2], OE[2]	n.a.

n.i. = No information; n.a. = not affected; ASD = atrial septal defect; VSD = ventricular septal defect; CPO = cleft palate only; CL/P = cleft lip and palate; PDA = patent ductus arteriosus; CHD = congenital heart defect; OE = occipital encephalocele; VUR = vesicoureteral reflux; RA = renal agenesis; FD = facial dimorphisms; CE = cloacal exstrophy; ARM = anorectal malformation; EA = esophageal atresia; OA/D = ovarian agenesis/dysgenesis.

[1] Diagnosed postnatally. [2] Diagnosed by prenatal ultrasonography. [3] No information on prenatal ultrasonography.

This scan also revealed partial agenesis of the corpus callosum and septum pellucidum, a low lying cerebellum, and a subcutaneous occipital cystic lesion with a diameter of 2.5 × 4 cm. A cranial magnetic resonance imaging (MRI) scan revealed that the content of the meningoencephalocele was primarily fluid with a small amount of impacted occipital cerebral cortex. Echocardiography showed a hemodynamically relevant perimembraneous VSD and a congestive cardiac failure. Following hemodynamic stabilization of the congestive cardiac failure, surgical repair of the encephalomeningocele with additional cysternotomy of the third ventricle was performed when the infant was 30 days old. Postoperatively, the infant developed progressive cerebral ventricular dilatation, which was controlled by ventriculoperitoneal shunting at the age of 2 months. Surgical repair of the hemodynamically relevant VSD was performed, and the infant was discharged from hospital at the age of 4 months.

Review of the Literature

We reviewed the English literature based on www.ncbi.nlm.nih.gov (June 25, 2009) on non-urinary tract anomalies in females with 47,XXX using the following search terms: 'superfemale', 'sex chromosomal disorder', 'sex chromosomal anomaly', 'sex chromosome aneuploidy', 'triple X (syndrome)', 'triplo X (syndrome)' and '47,XXX'. The results are summarized in table 1.

Discussion

The majority of 47,XXX females are reported as being healthy and having an unobtrusive phenotype. A number of reports, however, suggest that females with 47,XXX have an increased risk of urinary tract anomalies and ovarian dysfunction [3–6]. They are often reported to be of tall stature [2] and to have distinct phenotypic features such as hypertelorism and widely spaced nipples [7]. Neither of our cases displayed these phenotypic features at birth.

Atrial septal defects have been repeatedly associated with the 47,XXX karyotype. Other cardiac defects such as coarctation of the aorta and VSDs have also been reported, though less often [4, 8–13].

There have only been sporadic reports of gastrointestinal anomalies in females with 47,XXX [10, 14, 15]. These include anorectal and small intestinal malformations (table 1). One case of triple-X syndrome with jejunal atresia [16], and another with duodenal atresia [17] have recently been reported. In the patient with duodenal atresia, the pancreas was normal [17].

Only a few cases with structural brain anomalies have been reported among females with 47,XXX (schizencephaly, hydromyelia, hydrocephalus, occipital encephalocele and sacral meningomyelocele) [3, 18, 19]. There has only been one previous report of an encephalocele [4].

No study has systematically investigated a large sample of females with 47,XXX using an unbiased mode of ascertainment. Such a study would help to identify the malformations that are truly associated with this chromosomal aneuploidy. The large number of reports of urinary tract anomalies among females with 47,XXX, however, is strongly suggestive of a true association [4, 10]. Case reports may provide some degree of cumulative evidence for association with other malformations. This evidence should be taken into account upon prenatal identification of a 47,XXX karyotype. We consider this finding to be an indication for detailed fetal ultrasonography of multiple organ systems.

There is no obvious biological mechanism to explain the occurrence of malformations in females with 47,XXX. It has been shown, however, that more than one X chromosome is active in the majority of human triploid cells [20]. It has been suggested that the active X is selected by repression of its XIST locus: a dosage-sensitive repressor is encoded by an autosome, and the extra dose of this key repressor enables the expression of more than one X in triploid cells [20]. Since females with 47,XXX carry a normal set of diploid autosomes, it could be hypothesized that rare copy number variants in an autosomal repressor cause an increased expression of this repressor which results in more than one X chromosome being activated. This would have consecutive dosage effects on embryonic development and the formation of various congenital malformations. Since no autosomal repressor has yet been identified, this hypothesis cannot be experimentally validated at this time.

Conclusion

We have provided further evidence for an association of the triple-X syndrome with non-urinary tract anomalies. We conclude that the prenatal identification of a 47,XXX karyotype is an indication for detailed fetal ultrasonography of multiple organ systems. Such prenatal screening for possible associated congenital malformations should help to ensure optimal perinatal clinical management of 47, XXX cases.

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