

## Multiple Congenital Anomalies in a Filipino Infant with Trisomy X Syndrome

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### ABSTRACT

We present a Filipino infant with 47,XXX karyotype with multiple congenital anomalies consisting of cranial abnormalities, hypotonia, dysmorphic facies and hypoplastic right heart syndrome. This case provides additional data to the syndrome's limited phenotypic spectrum of defects described in previously reported cases.

*Key Words: trisomy X syndrome, developmental delay, facial dysmorphism, congenital heart disease*

### Introduction

The incidence of Trisomy X occurs in an estimated 0.8/1000 female births.<sup>1</sup> The first 47,XXX karyotype was described by Jacobs et al in 1959 in a woman of average intelligence who had secondary amenorrhea.<sup>2</sup> Since that time, over 200 cases have been reported but no consistent clinical pattern can be distinguished.

Aside from menstrual problems and mental deficiency which are the common reasons for consult in adulthood, few cases have been reported regarding the associated congenital anomalies in infancy.

Here we report on a Filipino female infant with a 47,XXX karyotype who had cerebral atrophy, global developmental delay, generalized hypotonia, unusual facies, complex cardiac malformations and cholelithiasis.

### Clinical Report

The patient was born full term by spontaneous vaginal delivery to an 18 year old primi gravida mother after an uncomplicated pregnancy. She was cyanotic at birth with no cry and activity until after 5 minutes of resuscitation. She had a birth weight of 2 kg which was below the 5<sup>th</sup> percentile.

She was cyanotic since birth with episodes of intermittency of feeding, fair activity and failure to thrive. No medical consultation was sought until 9 months of age when she had

a bout of pneumonia and was diagnosed to have a congenital heart disease. She also had global developmental delay.

At the time of examination at 1 year and 8 months old, she was fairly active and poorly nourished. Her head circumference was 42 cm which was below 2 SD<sub>s</sub> for her age. Likewise, her weight was below the 5<sup>th</sup> percentile (5.9 kg). But her length was 79 cm which was along the 90<sup>th</sup> percentile. Pertinent physical findings showed an enlarged open anterior fontanelle, plagiocephaly with frontal bossing, bitemporal depression, square-shaped face with hypertelorism, upslanted palpebral fissures, exotropia, broad nasal bridge with small nasal tip, anteverted nares, ears with prominent antihelices, a grade 3/6 holosystolic murmur on the left parasternal area with subcostal retractions and decreased breath sounds, a palpable liver at 3.5 cm below the right costal margin, hypoplastic labia majora and a sacral dimple. Limb anomalies included simian crease and clinodactyly of the 5<sup>th</sup> digit of both hands, 2<sup>nd</sup>-3<sup>rd</sup> toe syndactyly, with 3<sup>rd</sup> toe overlapping the 4<sup>th</sup> toe, digital clubbing and hypotonia (Figures 1A-B).

Chromosomal analysis of peripheral leukocytes showed a 47,XXX chromosome constitution in all cells (Figure 2). 2D echocardiography was compatible with a hypoplastic right heart syndrome. Chest X-ray showed consolidation and pleural effusion. Cranial CT scan revealed findings of cerebral parenchymal volume loss with ex-vacuo dilatation of ventricles, corpus callosum dysgenesis and closure of the metopic sutures. Abdominal ultrasound reported an incidental finding of cholelithiasis. Ultrasound of both kidneys and urinary bladder was normal. Pelvic ultrasound revealed an infantile uterus with no visualized ovaries, which was still acceptable for age.

### Discussion

A 47,XXX chromosome constitution usually presents with no characteristic somatic changes which would facilitate its clinical diagnosis. While a high proportion of cases were seen on account of mental or gynecologic disturbances, only little is known about the physical patterns of malformation associated with this chromosomal abnormality.

The clinical manifestations of Trisomy X individuals that have so far been reported were protean and had diverse associations with other abnormalities. Majority of the cases present with mental retardation, behavior/psychotic abnormalities, gynecologic problems and mild dysmorphisms

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Figure 1. A) Frontal bossing, bitemporal depression, hypertelorism, esotropia, depressed nasal bridge. B) clinodactyly of the 5th finger (with permission).



47, XXX  
Source: Cytogenetics Laboratory, Institute of Human Genetics

Figure 2. Chromosomal analysis showing an extra chromosome X.

only, like microcephaly, clinodactyly and obesity.<sup>3-5</sup> Of note, there have been structural abnormalities that were found to be usually occurring with this chromosomal abnormality, specifically that of genitourinary and lower mesodermal defects such as renal and anal agenesis, urinary tract malformations, sacral vertebral fusion defects, and ovarian and uterine dysgenesis.<sup>6-9</sup>

Still supporting the fact that this chromosome constitution presents with manifold manifestations, it has also been found in some autoimmune disorders like pure red cell aplasia,<sup>10</sup> systemic lupus erythematosus<sup>11</sup> and premature ovarian failure,<sup>12</sup> suggesting a possible role of chromosome X in regulation of immunity. Interestingly too, Trisomy X has been reported to occur simultaneously with other single gene disorders like Cockayne syndrome,<sup>13</sup> neurofibromatosis<sup>14</sup> and femoral hypoplasia -unusual facies syndrome.<sup>15</sup> Moreover, it has also been linked with mosaic Turner syndrome (45,X/47,XXX).<sup>16,17</sup>

Hood et. al. reported a case of Trisomy X, this time associated with multiple congenital anomalies consisting of urogenital defects, craniofacial abnormalities and tracheal agenesis sequence with laryngeal atresia and pulmonary hypoplasia. The unusual facial appearance in this report included a "square" face, persistence of forehead hair, hypertelorism, short philtrum, recessed chin, beaked nose and rudimentary formation of upper ear helices.<sup>18</sup> Although these facial features can be partly suggestive of a Potter sequence, Ballesta and Zapata proposed that certain facial changes including short palpebral fissures, midface hypoplasia, long philtrum, square chin and abnormal ears may be characteristic of the 47,XXX phenotype but their case series was small.<sup>19</sup>

Our patient shared some of the facial anomalies described in the above reports but differed in others. The midfacial and malar hypoplasia, hypertelorism and abnormal ears couldn't be attributed to Potter sequence as she did not have any renal or urologic abnormalities. The clinodactyly of the 5<sup>th</sup> digit was previously reported in earliest reports. However, to our knowledge, cerebral atrophy with generalized hypotonia, hypoplastic right heart syndrome, as well as cholelithiasis have been reported in literature. Cholelithiasis is uncommon in pediatric patients unless with predisposing factors. Whether this was contributed by the patient's diuretic use or something that is inherent in the syndrome remains to be elucidated.

A distinct etiologic relationship between congenital anomalies and 47,XXX phenotype has not yet been settled. Although it maybe true that cases exist in the general population without recognizable clinical abnormality, further clinical reports should be closely reviewed in order to establish a recognizable pattern of malformation for this chromosomal aneuploidy.

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