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Case Report

Triple X Syndrome with a Rare Finding: Cleft Palate

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ABSTRACT

Triple X syndrome (trisomy X) is a sex chromosomal anomaly caused by the presence of an extra X chromosome. The patients with Triple X syndrome have a wide range of phenotypic variability. Some individuals are only mildly affected or asymptomatic. Epicanthal folds, clinodactyly, tall stature and hypotonia are the most commom phenotypic features. Patients also may have seizures, genitourinary abnormalities and premature ovarian failure. We report a patient with Triple X syndrome and cleft palate. By describing this case, we want to draw attention to the association between cleft palate and Triple X syndrome.
Keywords: Triple X, trisomy X, cleft palate, seizure

Introduction

Triple X syndrome (47,XXX) is a sex chromosomal abnormality. Affected females have an extra X chromosome. This syndrome was described by Jacobs et al. (1). Incidence is approximately 1/10.000 females (2). There is a wide phenotypic variability of patients with triple X. Phenotypic findings include epicanthal folds, clinodactyly, tall stature and hypotonia. Also, clinical findings are seizures, genitourinary abnormalities, premature ovarian failure, intentional tremor, congenital hip dysplasia, constipation/abdominal pains (2,3). However, most of the woman with Triple X syndrome presents indistinct clinical signs. Herein, we report on a patient with Triple X syndrome and cleft palate (CP). Cleft lip and palate were described only in one paper describing two patients with Triple X syndrome. There is only one paper in the literature describing cleft lip and palate in two patients with Triple X syndrome (4). In the light of these findings, co-occurrence of cleft lip and palate and Triple X syndrome should be considered.

Case Report

A 11-year old girl was admitted to our neurology clinic with seizure. She was the second child of healthy unrelated parents. The age of mother at conception was 31 years old. There was no problem during the antenatal period and ultrasound scans were reported as normal. CP was identified in the first examination after delivery. She required 1 week of neonatal care for feeding difficulties. She was operated on for CP. She was able to sit without support at 8 months and walk without support at 14 months of age. She had delayed milestones in speech-language development. She pronounced her first words at the age of 3 years after speech therapy. She was able to produce her first sentences at 4 years of age. She also had mild learning disabilities and a poor academic performance. Wechsler Intelligence scale for Children-Revised was used for the assessment of her cognitive skills. Her verbal, performance and full-scale scores were 57, 79 and 66 respectively. There was no family history of either epilepsy or neurodevelopmental disorders. On physical examination, she was 133 cm (3 percentile) with a weight of

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27 kg (3-10 percentile) and a head circumference of 54.6 cm (50-98 percentile). She had a long face with an open mouth appearance (Figure 1, 2). She had received dental treatment. She did not have hypertelorism, epicanthal folds, clinodactyly, overlapping digits, pes planus or pectus excavatum.

The patient had generalized tonic-clonic seizure with a prolonged post-ictal period. Wake and sleep electroencephalogram showed normal background activity and no epileptic discharge. Brain magnetic resonance imaging was normal. Sodium valproate treatment was started and her epilepsy was well controlled. She was referred to a genetic department as her findings included CP, learning disabilities and seizure. Chromosome analysis using G-band technique revealed a 47,XXX karyotype (Figure 3). The fluorescent *in situ* hybridization analysis (FISH) of 22q11.2 locus was normal signal pattern with no deletion. After the diagnosis of Triple X syndrome, in order to investigate the abnormalities associated with this syndrome, an abdominal ultrasound and echocardiography were performed and both of them were normal. Genetic counselling was provided to the patient and her family. Her family was informed about the recurrence rate, which is estimated to be below 1%.

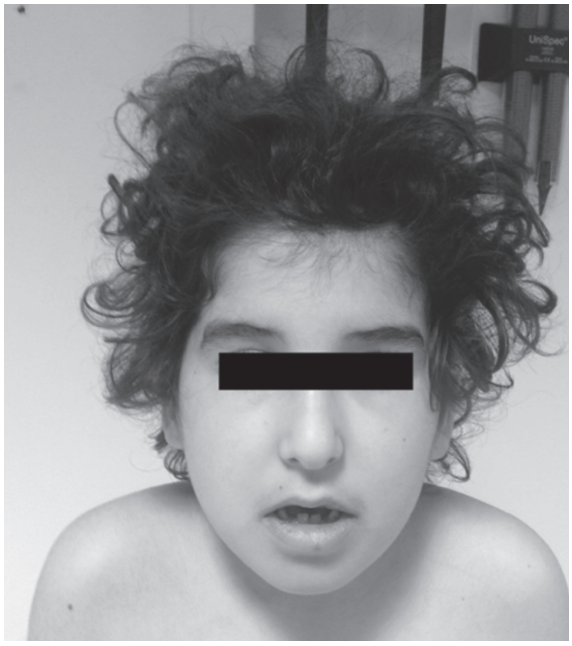

Figure 1. Patient with long face with open mouth appearance

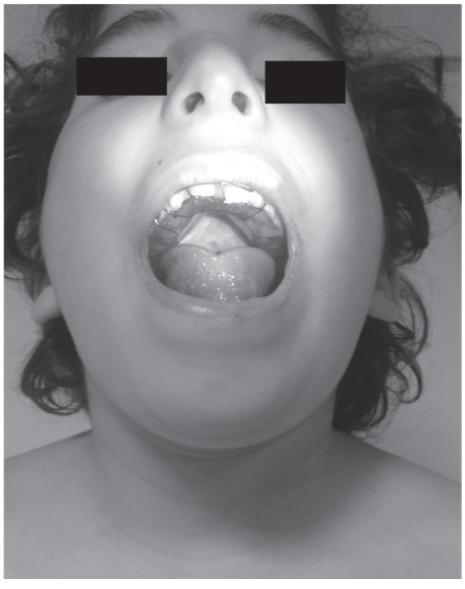

Figure 2. Patient with operated cleft palate

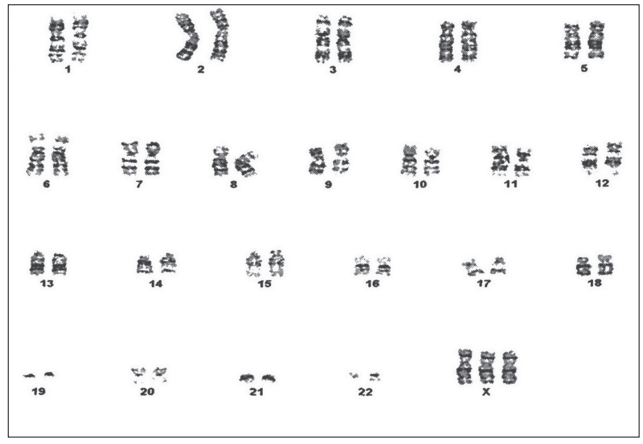

Figure 3. 47,XXX karyotype of the patient

Discussion

Triple X syndrome is the most common female chromosomal abnormality. Due to a nondisjunction event in the cell division, during gametogenesis or after conception, X chromosomes fail to properly separate resulting in a numerical abnormality. Triple X has a significant correlation with advanced maternal age (2). Most patients with Triple X syndrome are asymptomatic or mildly affected so approximately only 10% of patients are diagnosed (2). Minor physical findings including hypertelorism, epicanthal folds, up-slanting palpebral fissures, clinodactyly, overriding digits, pectus excavatum and pes planus can be seen (2,3). Genitourinary malformations including renal dysplasia, unilateral kidney, ovarian malformations, premature ovarian failure, primary amenorrhea and congenital heart defects such as atrial and ventricular septal defects, pulmonic stenosis and aortic coarctation have also been described (2). Seizure disorders can be seen in 15% of patients. Different seizure types including absence, partial and generalized tonic clonic seizures have been described but complex partial seizures are the most commonly seen type. A good response to standard anticonvulsant treatment has been described. The most preferred antiepileptic drugs are carbamazepine, sodium valproate and clobazam (2,5). Our patient also presented with generalized seizures and seizure control

was achieved with sodium valproate treatment. Patients with Triple X syndrome also have developmental and psychological problems in variable degrees. Early milestone delays in motor and speech-language development can be seen. Speech and language deficits can continue during the school and adolescent period (3). There is a wide variation in full-scale intelligence quotients of children with triple X ranging from 55-115 (2). Our patient also had mild learning difficulties. In cleft lip and CP, the upper lip and roof of the mouth are affected. When CP is associated with two or more malformations, then it is called syndromic CP. If it is isolated or cannot be associated with a recognizable pattern, it is called non-syndromic CP. Environmental and genetic factors may be responsible for cleft lip and palate. Several genes causing syndromic CP have been discovered. The T-box transcription factor-22 gene, located on chromosome Xq21, is important in the etiology of syndromic cleft lip and palate (6). Maternal smoking, maternal alcohol use, folate deficiency and anticonvulsant (phenytoin/hydantoin, valproic acid and topiramate) treatment during pregnancy are environmental factors associated with orofacial clefts. Palatal anomalies were found in approximately 70% of patients with 22q11.2 Deletion syndrome so the FISH of 22q11.2 locus was performed for our patient, a normal signal pattern with no deletion was detected. According to the Lyon hypothesis, one of the X chromosome in females is randomly selected and inactivated early in the embryonic development so each female has only one active X chromosome. But in the majority of human triploid cells, more than one X chromosome is active (7). Fryns et al. (8) and Ramaekers et al. (9) suggested that the over expression of genes located on the X chromosome may have a gene dosage effect and may cause the developmental anomalies in the genitourinary system of triple X patients. This presumed dosage effect may also be applicable as the genesis of CP. Previously, two Triple X syndrome cases with cleft lip and palate were defined (4). The first described report with triple X was a foetus; hydramnios, unilateral cleft lip and palate and also a sandal gap in both feet were detected prenatally at 26-27 weeks of gestation. Diagnosis was confirmed by karyotype and FISH analyses. The foetus was terminated and autopsy findings were compatible with the prenatal sonographic findings. Other features of this foetus were hirsutism, bronchogenic cyst, syndactyly, bilateral postaxial polydactyly, abnormal cervical vertebra and absent sacral tapering. Another reported case with Triple X syndrome was a 7-year-old girl with multiple congenital anomalies including curved bushy eyebrows, small palpebral fissures, a broad nasal bridge, a bilateral cleft lip and palate, camptodactyly, sacral meningomyelocele and bilateral talipes equinovarus. She had Grade III vesicoureteral reflux, recurrent urinary tract infections and mullerian abnormalities. Brain computed tomography revealed parietal bone agenesis. She had developmental delay and had been receiving speech therapy. There were differences between our case and that reported by Jagadeesh et al. (4), these two patients have multiple phenotypic and clinical findings, but our patient has indistinct clinical signs. The only similarity between our patient and the reported second case was a delay in speech development. Our case provides a rare example of Triple X syndrome with CP. We cannot conclude that there is a causal relationship between these two but we want to draw attention to the possible association between triple X and CP.

Ethics

Informed Consent: Was obtained from the patient and his parent.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., H.M.G., E.K., Design: E.G., H.M.G., E.K., Data Collection and Processing: E.G., H.M.G., E.K., Analysis and Interpretation: E.G., H.M.G., E.K., Literature Search: E.G., H.M.G., E.K., Writing: E.G., H.M.G., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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