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Title: Co-existance of Goldenhar and Klinefelter syndromes in a case born following ICSI

Running Title: Co-existance of Goldenhar and Klinefelter syndromes

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ABSTRACT

Background: Intracytoplasmic sperm injection is a widespread and powerful method enabling men with low sperm quantity and quality to become a father. But there are increased risks of many problems for the offspring such as congenital malformations, chromosomal abnormalities, infertility, epigenetic diseases, delayed neuropsychological development when compared with naturally conceived children.

Case report: We present a case of 6-year-old male patient born following ICSI (Intracytoplasmic Sperm Injection) with clinical and radiological features of Goldenhar syndrome as well as a history of the operation due to unilateral cryptorchidism. His karyotyping showed the chromosomal constitution of 47,XXY

Conclusion: Clinicians should be aware of the risks for the increasing number of patients born following ICSI to maximise children's health and welfare.

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INTRODUCTION

Goldenhar syndrome (Craniofacial microsomia) is a rare condition with congenital abnormalities. It includes a spectrum of malformations, primarily involving structures derived from the first and second branchial arches. Facial asymmetry, mandibular hypoplasia, preauricular or facial skin multiple tags and/or pits, auricular anomalies (in the size and shape of the external auricle to anotia) and hearing loss are the characteristic findings of this syndrome. Vertebral, renal, cardiac, and limb anomalies are also present in the clinical features. Most cases are sporadic and various etiologies have been implicated such as chromosome abnormalities, single gene mutations, vascular disruption, teratogens, and very rarely maternal use of assisted reproductive techniques (ART) (1).

CASE REPORT

The proband was a 6-year-old male referred to our clinic because of facial dysmorphism and bicuspit aorta (Figure 1). He was the first child of non-consanguineous parents. The mother and father were 26 and 34 years-old at the time of gestation, respectively. The pregnancy was induced by ISCI with ejaculated sperm in another center because of severe oligospermia. Amniocentesis was recommended at 16th week pregnancy, but the family didn't accept it. The patient was born at 26 weeks of gestation with caesarean section. The patient had a birth weight of 810 grs. When he was one-year-old the patient was operated due to right cryptorchidism. The stages of motor development were normal. On physical examination performed at our clinic the weight was 17 kg (3-10th centile), the height was 112 cm (25-50th centile), and the head circumference was 51.2 cm (25-50th centile). Dysmorphic features included prominent glabella, asymmetric face, right malarial hypoplasia, three skin tags in the left ear and one in the right ear, right microtia and cleft earlobe, upslanting palpebral fissures, broad nasal root, narrow ala nasi, prominent columella, short neck,

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shoulder asymmetry, bilateral 5th clinodactyly, bilateral partial cutaneous syndactyly between 2nd and 3rd toes, left testis was located in the inguinal canal. The child had normal brain MRI and abdominal ultrasound. Echocardiography showed bicuspid aortic valve. In auditory examination, conduction type hearing loss of right ear was detected. Skeletal radiographies revealed fusion in C6-C7 vertebrae, height loss in all cervical vertebrae and hemivertebrae in C5 and C6. Chromosomal analysis of the patient indicated 47,XXY, while the parents had normal karyotypes. Fluorescent in situ hybridization with X, Y alpha satellite probes showed no signs of mosaicism in the patient.

DISCUSSION

Intracytoplasmic sperm injection (ICSI) is a widespread and powerful method in ART and usually applied for the treatment of couples with male factor infertility. Several studies found that there was an increased incidence of aneuploidies, mainly of the sex chromosome aberrations among the ICSI conceived children(2). Subfertile men are considered to have higher rates of aneuploid offspring, secondary to gametes with higher rates of chromosomal segregation errors (3). Invasive nature of the ICSI procedure may also lead to embryonal aneuploidy by disruption of the oocyte meiotic spindle or nuclear decondensation of spermatozoa (4). Goldenhar syndrome is the first reported congenital anomaly followingART, although there are a few studies about Goldenhar syndrome following ICSI (5). To the best of our knowledge, this is the first report of a patient with co-existance of Goldenhar and Klinefelter syndromes conceived through ICSI. The exact mechanism is unclear. But altered gamete environment due to the hormonal stimulation, physical manuplation, and embryo culture during ICSI procedure may potentially initiate the changes such as epigenetic modifications in growth and development genes that are responsible for the such adverse outcomes (6, 7). Although these syndromes as an outcome of ICSI are rare, further studies are needed to understand the

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molecular basis not only for health care professionals, but also for the couples considering fertility treatment.

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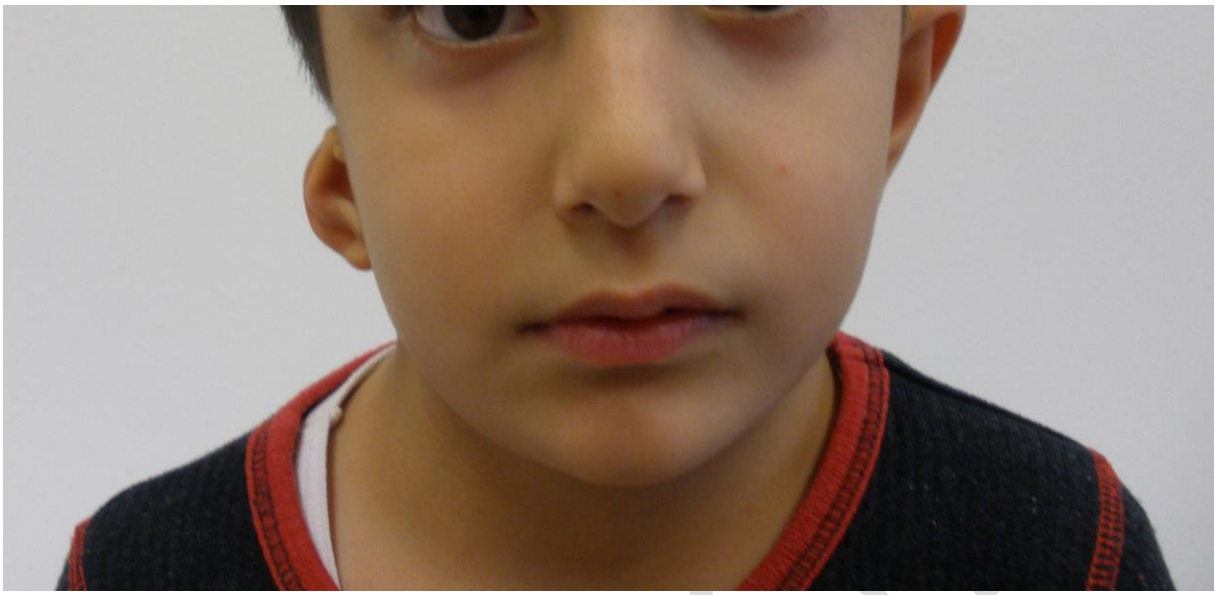

Figure 1a.

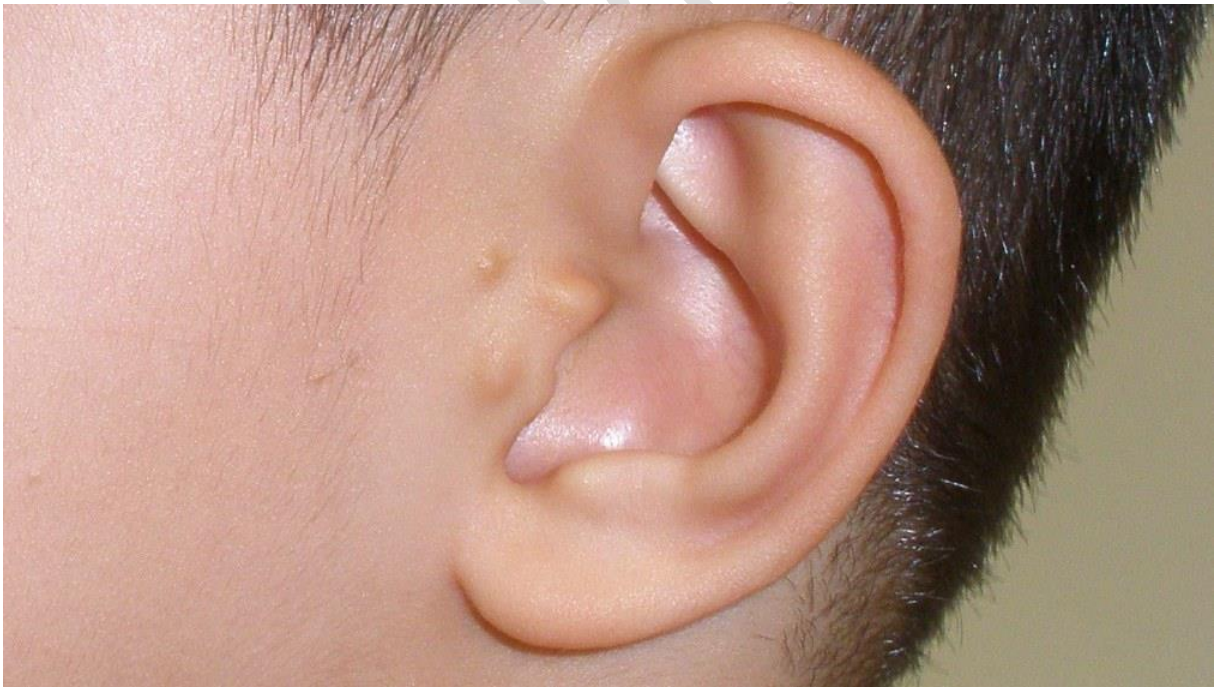

Figure 1b.

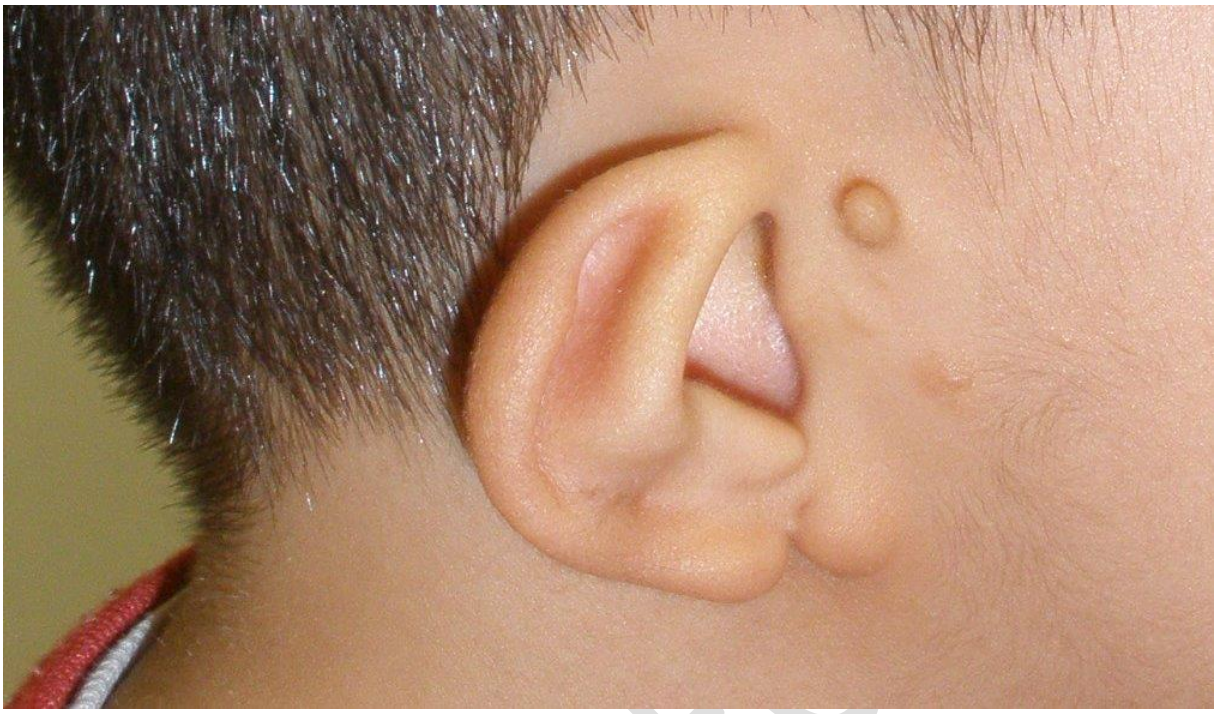

Figure 1c.

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