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Case report

Goldenhar syndrome associated with genital tract abnormality

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Accepted 3 August 2019

SUMMARY

Goldenhar syndrome, also known as *oculo-auriculo-vertebral syndrome*, has been described since 1952. Traditionally, the syndrome has been described as having eye, ear, facial and vertebral anomalies. However, numerous case reports and reviews have highlighted multi-organ involvement, including cardiovascular, gastrointestinal, respiratory system and urinary abnormalities. We describe a 13 years old who has a reproductive tract abnormality, which has not been reported previously as a finding of Goldenhar syndrome.

BACKGROUND

Goldenhar syndrome, also known as *oculo-auriculo-vertebral dysplasia*, is a disorder with craniofacial morphogenesis.¹ Several findings that are well described with Goldenhar syndrome include craniofacial abnormalities with hemi-facial microsomia (ie, one side of the face is smaller than the other), cleft lip and palate, mandibular abnormalities, eye abnormalities including epibulbar dermoids (vision may be impaired by involvement of the pupillary axis), colobomas, lid abnormalities, ear abnormalities including microotia (small ears), preauricular appendages (skin tags), hearing loss, skeletal abnormalities including vertebral abnormalities, renal defects, conotruncal cardiac defects and brain abnormalities.

The incidence of this syndrome, first described by Maurice Goldenhar in 1952,² is described between 1:3500 and 1:45 000.³ Originally, it was described as a triad of mandibular hypoplasia, epibulbar dermoid and pre-auricular skin tags.⁴ The ocular, auricular and facial defects are the most common

defects described in this syndrome.⁵ Previous reports have described maternal diabetes and increased risk of having Goldenhar syndrome,^{6, 7} and of multiple internal organ defects. Also, axial mesodermal dysplasia spectrum has been suggested to describe craniofacial microsomia and associated anomalies.⁸ The inheritance is thought to be multifactorial, although abnormal embryonic vascular supply disrupting the mesoblastic branchial and pharyngeal system has been thought to be a contributing factor.⁹ To date, an identified genital abnormality in a patient with Goldenhar syndrome has not been reported.¹⁰

CASE PRESENTATION

We obtained signed consent from our patient and her caregivers. Our patient was born at term to parents with consanguinity (first cousins). She was noted to have bilateral cleft lip and palate requiring primary lip closure at 7 months and palate repair at 1 year. She had pre-auricular skin tags that were removed, mandibular abnormalities, micrognathia, stenosis of the right ear canal, hearing loss and a right pelvic kidney (figure 1) with vesico-ureteric reflux. The ultrasound (US) images show the ectopic kidney in the right iliac fossa. A third-generation pedigree revealed a paternal uncle who lost two children with cerebral palsy but no previous history of another affected relative with the same condition.

She presented to our centre for mandibular reconstruction and dental surgery. She received a tracheostomy after a prolonged intubation episode following reconstruction surgery and needed several dental surgeries. These airway problems have been reported previously.^{11–14} She had several tooth abnormalities requiring recurrent surgery and procedures for correction. She was presented with primary amenorrhea at 12 years of age. Her mother reported development of breasts, followed by pubarche and adrenarche. At 13 years of age, she was noted to have Tanner V breast development and pubic hair and axillary hair. Her external genitalia showed labia majora and minora with urethral meatus and a vaginal dimple, instead of a regular introitus. She had no bulging masses in her introitus, as one would expect in the case of a hematocolpos. Her mother attained menarche at 12 years and her sister at 13 years. She was not on any medications that caused amenorrhea, with no history of galactorrhea, head ache or visual defects, and she denied having sexual activity.¹⁵

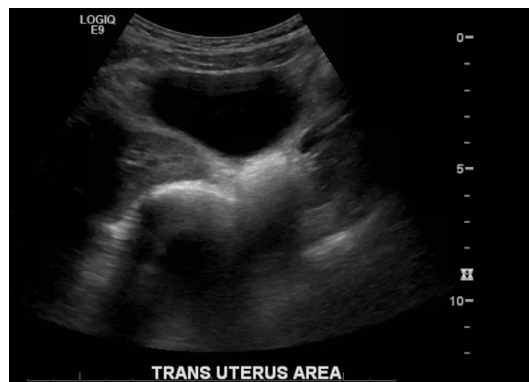


Figure 1 Ultrasound images show sagittal view of right pelvic kidney.



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To cite: Benjamin JC. *BMJ Case Rep* 2019;**12**:e230686. doi:10.1136/bcr-2019-230686



Figure 2 Pelvic ultrasound images show absence of uterus posterior to the bladder and presence of both ovaries.

INVESTIGATIONS

She had a negative human chorionic gonadotropin (HCG) test. The luteinizing hormone (LH) (4.3 mIU/mL) and follicle stimulating hormone (FSH) (2.5 mIU/mL) levels were both in normal range. Her TSH was 1.18. She had a prolactin level of 15.8 ng/mL. Her chromosomal testing showed normal female karyotype 46,XX. She underwent a pelvic US, which showed an absent uterus (figure 2). Her ovaries were of normal size with follicular pattern bilaterally. She was noted to have a simple free fluid structure adjacent to the left ovary. The US is limited in its ability to define structural abnormalities and MRI would better define soft tissue abnormalities. An MRI investigation is not an option as the patient has metal plates from a previous mandibular surgery. Due to association of a unilateral microtia, aural atresia and unilateral mandibular hypoplasia with an absent zygomatic

arch with TCOF1 missense variant (1084G>A) resulting in the substitution Ala362Thr¹⁶ and another study showing two individuals with Goldenhar syndrome with silent (Glu621Glu; Gln54Gln) TCOF1 sequence variants, TCOF1 gene mutation was searched; it was negative.¹⁷

DIFFERENTIAL DIAGNOSIS

Primary amenorrhea is failure of initiation of menses by the age of 14 years or by the age of 16 years with proper development of secondary sexual characteristics.^{18 19} It results from an interruption at any point in the hypothalamic–pituitary–ovarian axis (figure 3). Normal menses requires the anatomical presence of a genital tract and response of endometrium, 46,XX karyotyping and active support from other glands such as the adrenal and thyroid glands. There were no visual changes, galactorrhea and normal LH and FSH to suggest a central cause such as a *pituitary lesion* or a *prolactinoma*. In case of *ovarian failure*, she would have elevated LH and FSH levels. She had a negative HCG and denied sexual activity ruling out *pregnancy*. There was no thyromegaly and normal thyroid function tests (TFTs) ruling out *hypothyroidism* or *hyperthyroidism* as a cause for her amenorrhea. Her karyotype was normal 46,XX ruling out *Turner's syndrome*. With 46,XX karyotype, disorders of sexual development, present with varying degrees of virilization with excessive androgen exposure with *congenital adrenal hyperplasia*, and androgen exposure during pregnancy. Our patient had normal female secondary sexual characteristics. Patients with a 46,XY karyotype, could have female phenotype in *Swyer syndrome* with pure gonadal dysgenesis, where the patient has female external genitalia with undifferentiated gonads. With *androgen insensitivity*, patients have 46,XY karyotype with defect in the androgen receptor leading to female external phenotype, with a blind vaginal pouch, no uterus, ovaries or fallopian tubes with

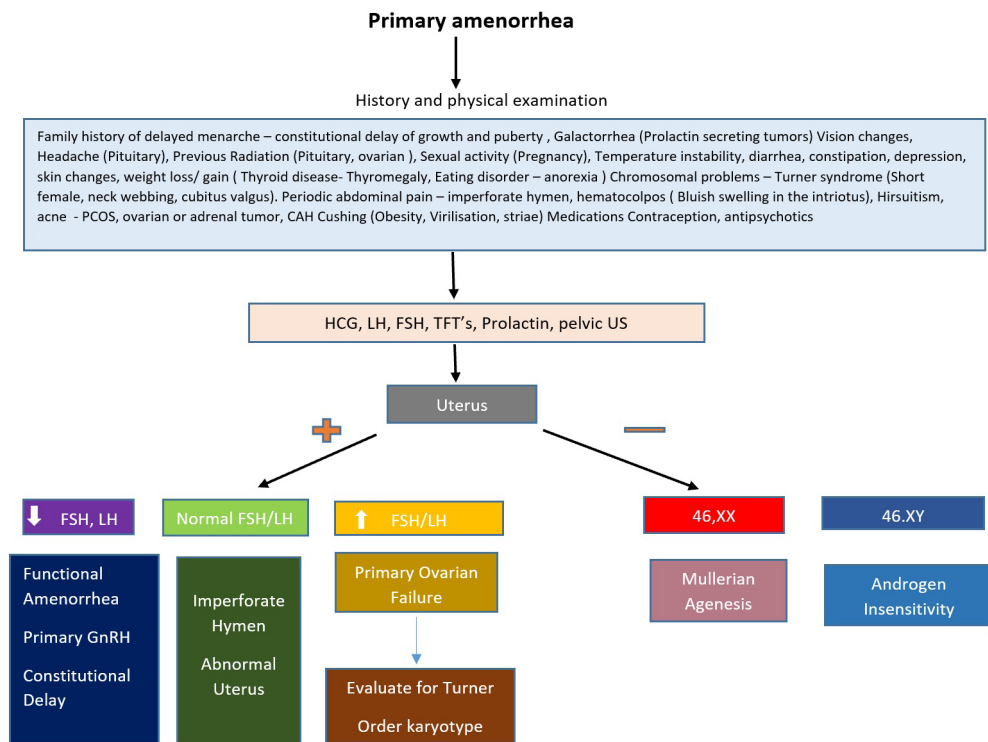


Figure 3 Approach to a patient with amenorrhea and differential diagnosis to consider based on investigations. CAH, congenital adrenal hyperplasia; PCOS, polycystic ovary syndrome; TFT, thyroid function test; US, ultrasound.

primary amenorrhea. A female karyotype of 46,XX excludes androgen insensitivity and pure gonadal dysgenesis, leading to the diagnosis of *Mullerian agenesis* as the cause of amenorrhea.

Our patient had normal LH and FSH levels, with 46,XX karyotype and an absence of uterus, suggesting Mullerian agenesis as the primary cause for amenorrhea. The female reproductive tract develops from a pair of Mullerian ducts forming the fallopian tube, uterus, cervix and upper two-thirds of the vagina. The ovaries and the lower third of the vagina are derived from the primitive yolk sac and sinovaginal bulb. The three phases in the development of the uterus are (1) organogenesis—when the Mullerian ducts are formed, (2) fusion—when the ducts fuse to form the uterine cavity and (3) septal resorption—resulting in a single cavity of the uterus. The most common classification system of Mullerian agenesis is that developed by the American Society of Reproductive Medicine.²⁰

Class 1 is characterised by Mullerian hypoplasia, and agenesis is due to early developmental failure of mullerian ducts at approximately 5 weeks of age, resulting in various degrees of hypoplasia of the uterus, cervix and upper two-thirds of the vagina. In agenesis, a uterus is not identified and small amounts of rudimentary tissue may be present. The most common form of agenesis is the Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome. It consists of a combined agenesis of the uterus, cervix and upper portion of the vagina. Symptoms may manifest at puberty as primary amenorrhea with normal secondary sexual characteristics, as ovarian function is preserved. The ovaries originate within the primitive ectoderm and not from the paramesonephros, and thus these patients have normal female sexual development. Renal anomalies occur in 29% of patients with Mullerian duct agenesis and are commonly associated with unicornuate uterus, rather than the other forms. Other renal anomalies include ectopic kidney, horseshoe kidney, renal dysplasia and duplicated collecting systems.²¹

TREATMENT

Our patient was managed by multidisciplinary team of specialists with multisystem involvement with Goldenhar. Her main input at our institution was with Orthodontics for mandibular distraction and reconstruction and recurrent dental procedures. She had a Furlow palatoplasty by plastic surgery. Audiometry revealed moderate–severe conductive hearing loss in the right ear with ear canal stenosis and normal hearing loss and middle ear dysfunction in the left ear. She was treated with a bone anchored hearing aid amplification device for her right ear. She was followed by otolaryngology for problems related to critical airway and received urgent tracheostomy which was decannulated with no complications. She had no complications from the pelvic kidney and has ongoing follow-up with urology and renal specialists. She is treated by pulmonology for mild obstructive sleep apnea. As for her uterine abnormalities, she was informed that she would be unable to carry a pregnancy and will need a surrogate carrier in the future. She is regularly followed by geneticist and paediatrician. She is receiving speech therapy for problems with articulation. She will be managed by gynaecologist for amenorrhea and will have an MRI in the future.

OUTCOME AND FOLLOW-UP

She is currently in main stream school with accommodations for her difficulties with hearing and articulation. She received speech therapy for articulation problems and is able to tolerate pureed solid feeds. She will continue to receive ongoing follow-up and support from the multidisciplinary team and various specialists.

She is due to have cranio-facial surgery correction of her facial abnormalities in the future.

DISCUSSION

Goldenhar syndrome has multifactorial inheritance. Our patient had no affected parents or siblings with abnormalities. When primary amenorrhea occurs with otherwise normal pubertal development, a structural abnormality of the Mullerian duct system should be suspected. Imperforate hymen is the most common disorder of the Mullerian duct abnormality and presents with periodic pain and a lower abdominal mass, which results in a blood-filled vagina called the *hematocolpos*; diagnosis is by inspection of the introitus, which shows the bulging hymen with a bluish discoloration. Our patient did not present with these findings. Instead, she had a vaginal dimple in place of the introitus and an absence of uterus was detected on US, suggesting MRKH syndrome, which is characterised by utero-vaginal atresia in an otherwise phenotypically normal female with a normal 46, XX karyotype. Anomalies of the genital tract in Mullerian duct abnormality can range from upper vaginal atresia to total Mullerian agenesis with urinary tract abnormalities.

Patient's perspective

I was diagnosed with Goldenhar syndrome when I was 3 years old. I have had numerous surgeries as a result of this condition. The hardest of these was having a tracheostomy, it was difficult to shower and to clean around tracheostomy. I could not play sports which made it very challenging. The pain from my mandibular surgery for extending my jaw and difficulty with eating was very hard too. They would turn the screw to extend by jaw bone and that was very painful. I was in the seventh grade when I first came to the USA and now I am in ninth grade and have adapted to school quite well. I do not think much about my ability to have children in the future, but my mother was re-assured to learn that I could still have children with the help of a surrogate carrier. Overall, I would say I am happy with school and the progress we have made with my treatment.

Learning points

- ▶ Goldenhar syndrome has multisystem involvement and needs the input of multidisciplinary providers to address different systems involvement. When a patient with Goldenhar presents with amenorrhea, scan for uterine abnormalities.
- ▶ Children with Goldenhar syndrome with craniofacial abnormalities are at increased risk for difficult intubation, which should be anticipated prior to major surgeries. Parents need to be advised about need for tracheostomy in such cases.
- ▶ School-aged children with Goldenhar syndrome will benefit from the input of speech therapist to help with articulation difficulties and for problems with mastication and chewing. These students are at increased risk for hearing loss and classroom accommodation such as preferential seating in front of class; hearing aids and school-based therapies help with optimal academic achievement in school.

Acknowledgements The author thanks Dr B Lee Ligon, Department of Pediatrics, Baylor College of Medicine, for editorial assistance.

Contributors The manuscript was compiled and written by JB, who is the named author.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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