Abstract: Frasier syndrome is a rare autosomal disorder characterised by pure gonadal dysgenesis and glomerulopathy. We report a case of frasier syndrome who presented with primary amenorrhoea.

Keyword: Frasier syndrome, gonadal dysgenesis, glomerulopathy, amenorrhoea

INTRODUCTION: Frasier syndrome is a rare autosomal dominant disorder first described in 46XY monozygotic twins in 1964. It is characterised by pure gonadal dysgenesis, progressive glomerulopathy usually FSGS.

CASE HISTORY: A 13 year old girl, third born of non-consanguineous marriage, studying in VII standard of low socio economic status with familial nephrotic syndrome came to the OPD for evaluation of the gonads. She had continuous, dull aching lower abdominal pain for past 1 year with passage of frothy urine on and off. No recurrent headache or visual disturbance. No history of seizures. No history suggestive of hypothyroidism (like hoarseness of voice, excessive weight gain, hypersomnia, cold intolerance). No history of any surgery in the past. No history of mumps or radiation exposure. She attained milestones at appropriate age and was appropriately immunized. Her school performance was good. Her bowel habits and sleep pattern were normal. First sibling died at 1 year of age, cause of death not known.
Second sibling had similar complaints, diagnosed to have nephrotic syndrome, she expired while being treated of renal failure at ten years of age. On examination patient was moderately built and nourished. Her height was 130cms and weight 29kgs. Her intelligence was fair, Vision-6/6. There was no pallor or pedal edema. Her cardiovascular, respiratory, central nervous system, ophthalmological and ENT examination were normal. Perabdomen was soft, hernial orifices were free and there were no inguinal swellings. External genitalia was female type and infantile. There were no markers of chromosomal aberrations.

DIFFERENTIAL DIAGNOSIS: Turner syndrome, Denys drash syndrome, Swyer syndrome.

INVESTIGATIONS:
- 24 h urine protein-3.2 g/dl
- S.Albumin -2.1 g/dl
- S.Globulin - 2.5 g/dl
- T.Cholesterol- 306 mg/dl
- USG abdomen and pelvis showed infantile uterus and streak gonads.
- Renal biopsy showed focal glomerulosclerosis.
- ECHO: Normal study.
- HORMONE STUDY:
  - FSH – 16 m IU/L
  - LH – 12 m IU/L
  - FSH – 16 m IU/L
  - LH – 12 m IU/L
  - TSH – 4.9 u IU/ml
  - PRL- 15 ng/ml
  - Genitogram: dilated roomy vagina visualized.
  - Cystoscopy: normal study
  - Genitoscopy: cervical impression noted with normal vaginal rugosities.
  - Diagnostic laproscopy: infantile uterus, fallopian tubes with fimbria, streak gonads at the end of fimbria.
  - No vas or testicular tissue made out.
  - Karyotyping: 46 XY karyotype.

DIAGNOSIS:
Diagnosis was based on the fact that karyotyping showed XY karyotype with renal biopsy showing focal glomerulosclerosis. So this is a case of pure gonadal dysgenesis with FSGS-FRASIER SYNDROME.

Turner’s syndrome is ruled out as the karyotype is 46 XY.
Swyer’s syndrome is ruled out as it has no renal manifestation.
Denys drash presents with nephroblastoma rather than FSGS.

FIG 3: KARYOTYPING
- TSH – 4.9 u IU/ml
- PRL- 15 ng/ml
- Genitogram: dilated roomy vagina visualized.
- Cystoscopy: normal study
- Genitoscopy: cervical impression noted with normal vaginal rugosities.
- Diagnostic laproscopy: infantile uterus, fallopian tubes with fimbria, streak gonads at the end of fimbria.
- No vas or testicular tissue made out.
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Estradiol – 53 pg/ml Testosterone -0.13 ng/dl
FIG 4: ABSENT AXILLARY HAIR

DISCUSSION:
Frasier syndrome may be either of the following two forms.
Classical form - 46 XY Karyotype

Rare form - 46 XX Karyotype. WT – 1 gene is a tumour suppressor gene in Chromosome 11 p 13.

FUNCTIONS: Encodes transcription factors that play a key role in maturation of genitourinary tract. Of particular interest are two alternative splice donor sites at the end of exon 9, leading to the insertion or omission of three amino acids between zinc fingers 3 and 4.

SPECTRUM OF DISORDERS WITH WT-1 MUTATION: WAGR SYNDROME:
Wilms tumor, Aniridia, Genital anomalies, Mental retardation

DENYS DRASH SYNDROME:
Wilms tumor, diffuse mesangial glomerulosclerosis, male pseudohermaphroditism

FRASIER SYNDROME:
Focal segmental glomerulosclerosis
Gonadal dysgenesis.

MOLECULAR DEFECT IN FRASIER SYNDROME:
Heterozygous point mutation in the donor splice site in exon 9 of Wilms tumor gene leading to loss of three amino acids (KTS isoforms), thus disrupting the normal ratio of +KTS/-KTS isoforms critical for proper gonadal and renal development.

KTS ISOFORMS AND TESTICULAR DIFFERENTIATION:
- KTS isoform
It induces gonadal ridge formation through proliferation of the coelomic epithelium, bipotential gonad.
+KTS isoform
It activates the transcription of the SRY gene located on Y chromosome, induces the expression of anti-mullerian hormone by the developing Sertoli cells.
Expression of the anti-mullerian hormone in the developing testis results in formation of seminiferous cords, allowing sex-specific gonadal development, and regression of mullerian structures.

CLINICAL FEATURES OF FRASIER SYNDROME:
Progressive glomerular nephropathy
46 XY Individuals have sex reversal, primary amenorrhoea (hypergonadotropic hypogonadism) and absent secondary sexual characters.
46 XX Individuals have normal ovaries, internal and external genitalia.

MANAGEMENT: In 46 XY Individuals’
Bilateral gonadectomy [prophylactically to prevent gonadoblastoma].
Low dose Estrogen-conjugated equine estrogen 0.625mg/day to initiate, mature and maintain secondary sexual characters.
Progestrone supplementation - to prevent unopposed estrogen stimulation of endometrium and to induce menstruation.
Management of nephrotic syndrome, irrespective of the karyotype.

REFERENCES:

2. Reddy J, Licht J: The WT1 tumor suppressor gene, how much do we really know?