An Unusual Case of Primary Amenorrhoea

RCOG World Congress 2017, Cape Town
Paediatric and Adolescent Gynaecology

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Declaration of Interests - None
Case Presentation

Background

- 18 year old
- Columbian ethnicity
- Maternal Pregnancy
  - Pre-eclampsia
  - No known exposure to teratogens including DES
  - SVD in UK
  - Birthweight 3kgs
- No reported clitoromegaly or genital ambiguity at birth
- Uneventful neonatal and infant period
Case Presentation

Childhood

- Recurrent Urinary Tract Infections (UTI) from age 3
  - Predominantly Pseudomonas and Gram Negative Bacilli
- Age 5 -7
  - Renal ultrasound scan, MAG3 isotope and DMSA scans
  - Duplex system on the right side
  - Trimethoprim nocte prophylaxis
  - Age 7 – no further UTI and discharged
- Age 11
  - Breast bud development and adrenarche
Family History

- Parents not consanguineous, only child
- Mother
  - Height 148cm
  - Menarche age 14
- Father
  - Height 152cm, Unknown age of puberty
  - Family history of short stature
- Paternal half sister
  - Age 25, height 152cm
  - Menarche age 11
  - SVD of healthy baby boy
Presentation at 14 years

General Practitioner

- Age 14
  - Arrested breast development
  - Amenorrhoea
  - FSH 52.6 iu/L and LH 15.7 iu/L
- Transabdominal Ultrasound scan
  - Ovaries not clearly visualised
  - Uterus could not be seen
- Referred to Paediatric Endocrinologist
Examination age 15

Paediatric Endocrinologist

- Ht 151cm and Wt 58.1kg
- Café au Lait Lesion right forehead and behind right ear
- No other peripheral stigmata or dysmorphic features
- Normal systems examination
- Pubertal rating P2, B3 and M0
- Normal external genitalia
- Vaginal dimple
Investigation

Blood results

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>64.3 iu/L</td>
</tr>
<tr>
<td>LH</td>
<td>19.6 iu/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>131 miu/L</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>&lt; 44 pmol/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>&lt; 0.1 nmol/L</td>
</tr>
<tr>
<td>DHEAS</td>
<td>2.8 umol/L</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>2.0 nmol/L</td>
</tr>
<tr>
<td>17 OH progesterone</td>
<td>2.0 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.84 mIU/L</td>
</tr>
<tr>
<td>FBC</td>
<td>Normal</td>
</tr>
<tr>
<td>LFT, U&amp;Es, Bone profile</td>
<td>Normal</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Normal</td>
</tr>
</tbody>
</table>

[Diagram showing hormone pathways from Adrenal and Ovary to other hormones like DHEA, Oestrone, TESTOSTERONE, OESTRADIOL, etc.]
Investigation

Cytogenetics - CGH

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karyotype (PBM) array CGH</td>
<td>del (1-22,X)x2</td>
</tr>
</tbody>
</table>

[Diagram of karyotype]
Investigation

MRI – before oestrogen

Abdominal and Pelvic MRI
- Absent uterus
- Absent cervix
- Ovaries not seen
- Rudimentary vagina
- Normal kidneys, bladder and urethra

DIAGNOSIS
Possible Rokintansky Syndrome AND Ovarian Dysgenesis
Clinical Progress

Transition

- Age 15
  - Started on Evorel 25 μg (Estradiol) patch twice weekly to complete pubertal development
  - 6 monthly increments of 25 μg to 100 μg
- Age 16
  - Care transitioned to specialist POI clinic
  - DEXA - osteopenia
- Age 17
  - Evorel 100 μg – switched to oral oestradiol 2mg
- Age 18
  - Repeat MRI
Investigation

MRI – after 3 years oestrogen

Abdominal and Pelvic MRI
Absence uterus
Absence cervix
Rudimentary vagina distal to introitus
Normal kidney position

DIAGNOSIS
Rokitansky Syndrome AND Ovarian Dysgenesis
Investigation

MRI – after 3 years oestrogen

DIAGNOSIS
Rokitansky Syndrome AND Ovarian Dysgenesis
Current and future progress

Age 18

• Long term follow up and support
  • Psychosexual support and counseling
  • Neovagina - vaginal dilation with specialist nurse
  • Fertility
  • Bone and Cardiovascular health
• Enrolled in a study for next generation WES
• Screen parents for renal and uterine anomalies
EMBRYOLOGY

PRIMITIVE HINDGUT

INTERMEDIATE MESODERM

ENDODERM AND ECTODERM

UROGENITAL SINUS

UROGENITAL FOLD AND GENITAL TUBERCLE

PGC

GENITAL RIDGE

MULLERIAN DUCTS

FALLOPIAN TUBES

UTERUS

CERVIX

UPPER 2/3 VAGINA

LOWER 1/3 VAGINA

EXTERNAL GENITALIA

Day 18-19

Day 28-36

Day 44-49

RENAL SYSTEM

EXTERNAL GENITALIA
Discussion

MRKH

• Eugonadal condition
• Represents a spectrum of congenital anomalies of the Mullerian tract
• 46XX karyotype
• Previously seen as a sporadic female-specific disorder
• May be autosomal dominant
• WNT4 and HOXA genes have been implicated in this condition
• Both these genes are important for organogenesis
Ovarian Dysgenesis

- Ovarian dysgenesis
  - disrupted formation of the primordial oocyte pool
  - or abnormal ovarian differentiation
- Estimated that 70% of cases are a result of Turner, X0/XX or other X chromosomal structural abnormalities
- 46XX ovarian dysgenesis is rare
- Often inherited in an autosomal recessive manner
- A number of gene mutations have been implicated in humans including in the genes FSHR, CYP19A1, NR5A1 and PSMC3IP
Discussion

Literature

- MRKH is rare (≈ 1 in 5000)
- Ovarian dysgenesis is rare (≈ 1 in 8000)
- Extremely rare for both to occur concurrently
  - 25 reported cases
  - Of which 15 were reported to have normal 46XX karyotype
  - Of which 15 had absent uterus
- Theories
  - Mutation of ‘truncal’ genes
  - Very small X chromosome microdeletions
  - Mosaicism within mesoderm
  - Other endocrine disruptors
- 100,000 Genome Project
## Discussion

### Genetics

<table>
<thead>
<tr>
<th>GENE</th>
<th>Organogenesis</th>
<th>Renal Development</th>
<th>Mullerian Development</th>
<th>Ovarian Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF1</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>WT1</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>WNT4</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td>HOXA</td>
<td>YES</td>
<td>YES</td>
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<td>NO</td>
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<tr>
<td>FSHR</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>CYP19A1</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>
Discussion

Genomics

• There is an improved understanding of the genetic basis of both of these conditions

• Whole exome sequencing is now cheaper and more readily available allowing us to move away from the candidate gene approach

• We are performing next generation exome sequencing in our patient and her family members, with particular emphasis on the WT1, SF1, WNT4 and HOXA genes