**Precocious pseudo-puberty presenting with bilateral ovarian involvement and progressing to juvenile granulosa cell tumor in a 2-year-old girl**

**Backgroun**

Feminising precocious pseudo-puberty in McCune-Albright syndrome (MAS) and juvenile granulosa cell tumour (JGCT) arises from bilateral and unilateral estradiol hypersecretion respectively. GNAS mutations cause MAS but have been also been described in some cases of JGCT.

**Aim**

To describe an unusual case of precocious pseudo-puberty and discuss the overlap between two entities: the McCune Albright syndrome and juvenile granulosa cell tumor.

**Case**

A girl aged 2.17 years presented with isolated bilateral breast development.

Past history: Birth weight: 3650 g, birth length: 50 cm 
- Parents unrelated, no relevant family history.

Examination - Weight: 13.2 kg (+1SD), Height: 94 cm (+2.6 SD) 
- Tanner stage: B3P2A1 
- Parental heights: Mother: 160 cm, Father 174 cm. 
- Midparental height: 160.5 cm (-0.4 SD) 
- Single « café au lait » patch on the antero-lateral border of the left thigh, 3cm in its largest axis, with irregular outline. 
- No bony deformity 
- Liver edge 7 cm below costal margin, no splenomegaly, no other significant findings.

Investigations 
- Estradiol: 18 pg / ml 
- Bone age: 5 years 
- No other significant findings 
- No bony deformity 
- Liver edge 7 cm below costal margin, no splenomegaly, no other significant findings.

Pelvic ultrasound (Fig 1, Fig 2):
- Right ovary: Enlarged, 66 mm in longitudinal axis, multiple cysts, (maximum 33mm) with thin septa 
- Pelvic MRI (Fig 4) 
  - Well defined solid-cystic abdomino-pelvic mass (5 x 10 x 12 cm) with left ovarian origin and extending to aorta and kidney 
  - No local invasion 
  - Normal right ovary 
  - Ureter: 4 x 2 x 0 mm 
  - Endometrium: 10 mm 

Pelvic ultrasound (Fig3)
- Left ovary: Enlarged, 63 mm in longitudinal axis, multiple cysts (maximum 38 mm) with thin septa

Provisional diagnosis: McCune Albright syndrome ([screening of anomalies associated with MAS (serum phosphate, calcium, IGFB, TSH, free T4, urinary free cortisol, bone scintigraphy)] - negative]

Treatment: Tamoxifen 20 mg daily. 

Progress: 
- After only 1½ months: 
  - 4 cm increase in height, Tanner stage: B3-A4 
  - Menorrhagia, Bone age: 6.5 years 
- Further investigations: 
  - LH RH stimulation test 
  - LH: 2.49 mIU / ml 
  - FSH mIU/ml: <0.1
  - LH mIU/ml: 0.15 

Further findings:
- Right ovary: Enlarged, 66 mm in longitudinal axis, multiple cysts (maximum 33mm) with thin septa
- Pelvic MRI: no other significant findings.
- Histopathology of tumour specimen (Fig 6):
  - Large cells with abundant eosinophilic cytoplasm and large hyperchromatic nuclei with many abnormal mitoses
  - Very polymorphic architecture, most often solid, richly vascularized with some hyaline and haemorrhagic foci.
  - Several Call-Exner bodies
  - No capsular infiltration
  - Immunochemistry: inhibin B+++ α-fetoprotein and anti-CD30 below the detection limit

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Genetic studies in tumour:
- GNAS mutation negative for the common hotspot (P201C, R201H and Q227L).
- Sequencing of exon 3 in AKT1 gene is pending (laboratory of Prof Velia, Paris).

Post-operative progress
- Immediate regression of menorrhagia 
- Estradiol: 18 pg / ml 
- Review aged 3 years and 4 months 
  - Height: 113 cm (+ 0.9 SD) 
  - Weight: 17.2 kg (0 SD) 
  - Pubertal stage: B1 P1 
  - Hormonal profile: 
    - Estradiol: 13 pg / ml, FSH: 2.52 mIU / ml, LH: 2.46 mIU / ml 
    - Pelvic ultrasound: no abnormalities

Discussion

-McCune Albright syndrome (MAS): somatic mutation of GNAS gene1 which encodes the G-protein α subunit, affecting tissues (e.g. skin, ovary, bone) in a mosaic pattern. 
  - Café au lait patches, precocious pseudo-puberty, fibrous dysplasia. 
  - More rarely hyperthyroidism, Cushings’s syndrome, gigantism and renal phosphate wasting

Genetic testing is unnecessary in classic cases (multisystem involvement) but single organ McCune Albright syndrome may require tissue biopsy and DNA analysis for confirmation 1.

-Juvenile granulosa cell tumor (JGCT): 67% of the sex cord-stromal tumours, 5-12% of all ovarian tumors in children.

Clinical presentation:
- Abdominal mass; isosexual precocious pseudo-puberty, disturbance of menstrual cycle +/- signs of hyperandrogenism in adolescents; acute abdomen (torsion of the annex, or tumor rupture with haemo-para-teritis).

Inhibin B and Anti-Mullerian Hormone levels are raised, and are useful in tumour monitoring.

GNAS mutation: found in 9 of 30 patients with JGCT2. Activating oncogene AKT1 mutation in more than 60% of cases.

The case we report is unusual. Feminising precocious pseudo-puberty was associated initially with evidence of bilateral ovarian activity, which then progressed to a juvenile granulosa cell tumor in one ovary with normal ultrasound and MRI findings in the other ovary.

The diagnosis of McCune Albright syndrome cannot be supported in our patient at present since she has only one café au lait patch, no bony lesions, and no GNAS mutation detected in DNA extracted from paraffin blocks of the ovarian tumor.

While the radiological and histological diagnosis of juvenile granulosa cell tumour is secure this does not explain the initial features at presentation in our patient.

The current diagnosis therefore is one of pseudo-puberty of ovarian origin, with progression to juvenile granulosa cell tumour, in which the underlying mechanisms remain unclear.

References