Successful medical management of severe neonatal Cushing syndrome with metyrapone, guided by mass spectrometry monitoring

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Background

Neonatal Cushing syndrome is a rare and severe condition, mostly associated with the McCune-Albright (MCA) syndrome. Management options include medical treatment (with ketoconazole or metyrapone resulting in 11-beta-hydroxylase blockade) and radical treatment with bilateral adrenalectomy. Spontaneous regression in late infancy has been reported.
We report on the outcome of a 14 month-old girl with severe neonatal Cushing syndrome on long-term treatment with metyrapone.

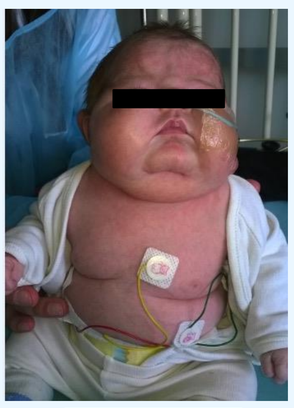
Clinical presentation

- Girl born with severe growth restriction (-4DS for height and weight)
- Neonatal hyperglycaemia requiring insulin treatment during 1 month
- At the age of 2 months :
  - growth arrest
  - clinical Cushingoid features
  - elevated circadian cortisol > 1000 nmol/L
  not suppressible by dexamethasone and
  undetectable ACTH levels.

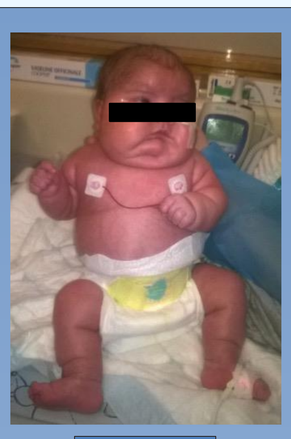
→ Severe ACTH independentCushing syndrome

Complications :
- Hypertension requiring 3 medications
- Hypotonia
- Immune depression resulting in Pneumocystis infection.

No other features of the Mc Cune Albright syndrome



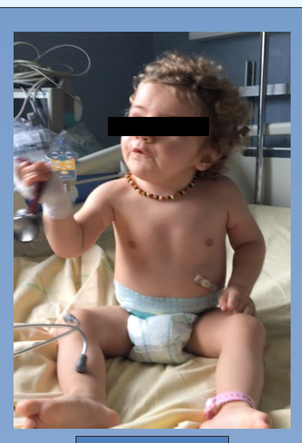
3 month old
Before treatment



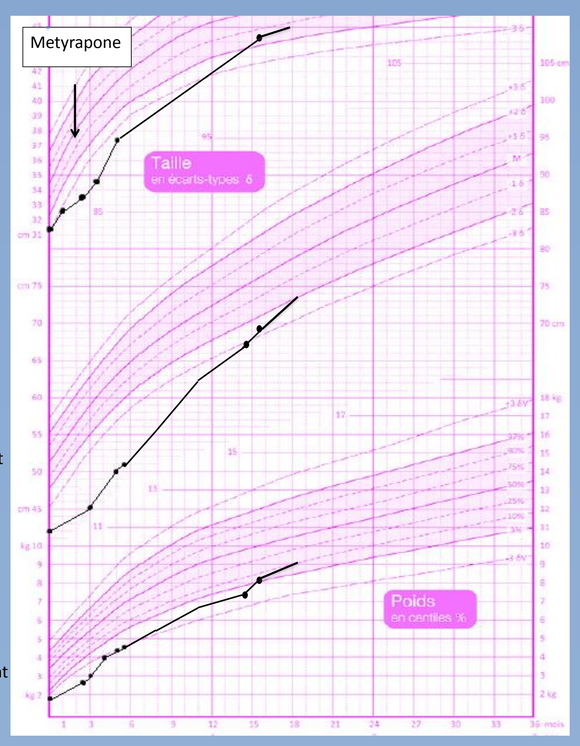
4 month old
M1 treatment

8 month old
M5 treatment

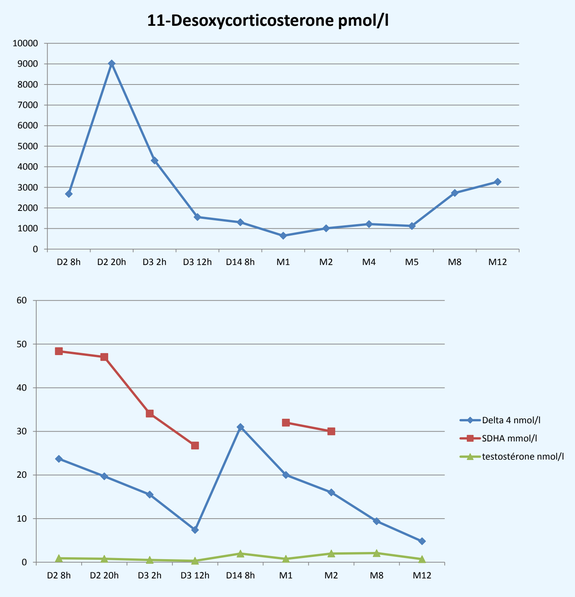
11 month old
M9 treatment



18 month old
M16 treatment



Evolution of hormonal markers by UPLC-MSMS



Therapeutic challenge

2 options :
-Radical treatment = Bilateral adrenalectomy, but irreversible
- Medical treatment with metyrapone : 11ß hydroxylase blockade

We chose the metyrapone, administered by nasogastric tubing, initiated at the dose of 80 mg every 6 hours.

Evolution

At the age of 18 months, hypercorticism was controlled with catch-up growth, disappearance of Cushingoid features, normal blood pressure and no clinical hyperandrogenism. Adrenal imaging showed persistently enlarged adrenals.

Diagnostic challenge

- Search for activating mutation of the GNAS gene in PBMC DNA: negative
- Sequencing of several genes involved in adrenal function (MC2R, ARMC5, PRKAR1A): normal
- But at 18 months:
  - signs of estrogenic impregnation without vaginal bleeding
  - ovarian cyst of 3 cm and stimulated uterus

→ **McCune Albright syndrome**

Conclusions

Long-term treatment of severe neonatal Cushing syndrome with metyrapone is efficient, well tolerated and can avoid bilateral adrenalectomy in transient cases. Mass spectrometry (UPLC-MSMS) for monitoring steroid changes is needed. This ultra specific method avoids overestimation of actual levels related to crossreactions between steroids.

References

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The authors have no interest to disclose

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