MULTIPLE MALFORMATIONS EXTENDING THE PHENOTYPIC SPECTRUM OF ANTYLE-BIXLER SYNDROME IN A PATIENT WITH P450 OXIDOREDUCTASE DEFICIENCY DUE TO TWO NOVEL MUTATIONS OF THE POR GENE

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Background
P450 oxidoreductase (POR) deficiency (PORD) is characterized by glucocorticoid and sex steroid deficiency and skeletal malformations, resembling Antley-Bixler syndrome (ABS; MIM 124015), a skeletal malformation phenotype also present in patients with fibroblast growth factor receptor 2 mutations (FGFR2; MIM 176394).

While genetic testing confirms both conditions, establishing the exact diagnosis on clinical grounds can be challenging.

Case Report
- Second child of non-consanguineous parents. (BMJ) J2-4 0:05, OFC 35.5cm.
- Facial features: abnormal scalp shape with very large anterior fontanelle, micropenis hypoplasia, flat nasal bridge, proptosis, and maxillae, small ears with thinned helices and absent auricular notches.
- Neurosurgery 2/5 - 4 tempo-sphenoid dysplasiameunio - closure (3), Arnold Chiari malformation, ventriculomegaly – right VPS.
- Midline synostosis right maxillary bones on skull.
- Ambiguous genitalia: female external genitalia, palpable labial tedacies.
- Urinary system: normal, renal pelvis.
- Rhabdomyolysis, 11 months old.
- Her younger sister was healthy and unaffected.

Methods
Ultrasound scan (USG) survey (brain, pelvic):

Skeletal survey:

Molecular genetic analysis of the POR gene:
- compound heterozygosity for a novel missense mutation p.A207T;
- novel intron c.1248+1G>T mutation, predicted to cause aberrant mRNA splicing.

Karyotype: 46, XY

Hormonal analyses:
- A short synacthen test (SST) - adrenal insufficiency and the patient was started on hydrocortisone replacement.

Urinary steroid profiling by gas chromatography mass-spectrometry (GC/MS):
- showed combined 21-hydroxylase and 17alpha-hydroxylase deficiencies, indicative of POR.

Discussion
- Cytochrome P450 oxidoreductase - flavoprotein that donates electrons to all microsomal P450 enzymes, including the steroidalogenic enzymes 3P450, 11P450, 17P450, 20P450, 21P450, and 25P450.
- The human POR (OMIM #170770) gene maps to chromosome band 16p13.3; from base pairs 73,915,410 to 73,986,851 (17,754bp).
- Antley-Bixler Syndrome (POR deficiency) is an extremely rare disorder with impaired steroligenes and skeletal anomalies and evidence of homeostasis or combined heterozygous mutations in the gene encoding cytochrome P450 oxidoreductase (POR; 170770) on chromosome 16p13.3.
- Autosomal recessive inheritance.
- Mortality of 80% at prenatal period due to severe respiratory depression and decreasing with increasing age [3].
- Overlap phenotypes: POR or POR/PR2 gene mutations will distinguish the entity [1, 2].
- More frequent occurrence of genital malformations in patients with impaired steroligenes and All Syndromes [6].
- Treatment of manifestations:
- Prevention of secondary complications - major may be at risk for adrenal insufficiency and Addisonian crisis, especially at times of severe febrile illness or major surgery [5, 6].
- Prenatal diagnosis in further pregnancies;

Conclusions
This case of PORD presented with complex malformations rarely observed in PORD and more typical for FGFR2 mutations while 46,XY ISS was associated with PORD.

References