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

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Abstract

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 malformaton phenotype also present in patients with fibroblast growth factor receptor 2 mutations (FGFR2, MIM 176943). While genetic testing confirms both conditions, establishing the exact diagnosis on clinical grounds can be challenging.

Objective and hypotheses: To characterize cause of disease in a patient with 46,XY DSD and complex malformations.

Methods: A now 2 year-old child of non-consanguineous parents was investigated immediately after birth for 46,XY DSD (female external genitalia, palpable labial testicles) and complex malformations, including ABS (craniosynostosis, midface hypoplasia, arachnodactily, rocker-bottom feet, bilateral talipes), spinal dysraphism and right bronchial stenosis. We performed hormonal investigations, urinary steroid profiling by gas chromatography mass-spectrometry (GC/MS) and genetic analysis of the *POR* gene.

Results: A short synacthen test revealed adrenal insufficiency and the patient was started on hydrocortisone replacement. 17OHP was moderately elevated (20.6 nmol/L). Urinary steroid profiling at 2 months of age showed combined 21-hydroxylase and 17alpha-hydroxylase/17,20 lyase deficiency, indicative of PORD. *POR* gene analysis revealed compound heterozygosity for a novel missense mutation p.A200T and a novel intronic c.1248+1G>T mutation, predicted to cause aberrant mRNA splicing. The child was raised as a girl and gonadectomy was performed at 11 months of age. Shortly thereafter the mother fell pregnant again and GC/MS analysis of maternal urine confirmed that the foetus was unaffected; the mother subsequently delivered a healthy baby.

Conclusion: This case of PORD presented with complex malformations rarely observed in PORD and more typical for *FGFR2* mutations while 46,XY DSD indicated PORD. GC/MS analysis reliably detects PORD in affected children and can help with prenatal diagnosis in further pregnancies. Assessment of adrenal function should be part of the early investigations in complex DSD.

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 malformaton phenotype also present in patients with fibroblast growth factor receptor 2 mutations **(FGFR2, MIM 176943)**.

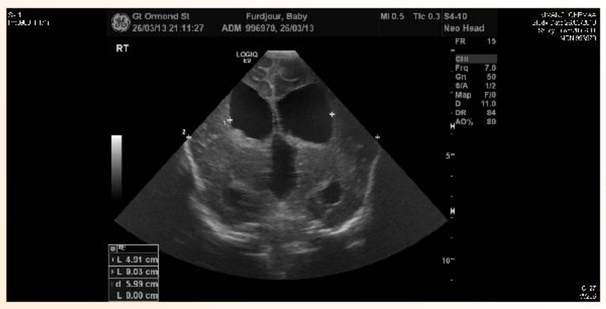
While genetic testing confirms both conditions, establishing the exact diagnosis on clinical grounds can be challenging.

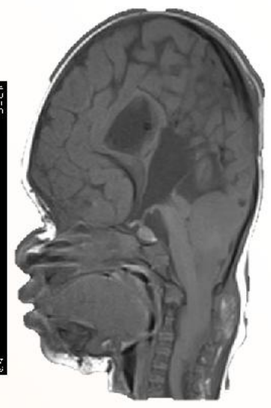
Case Report

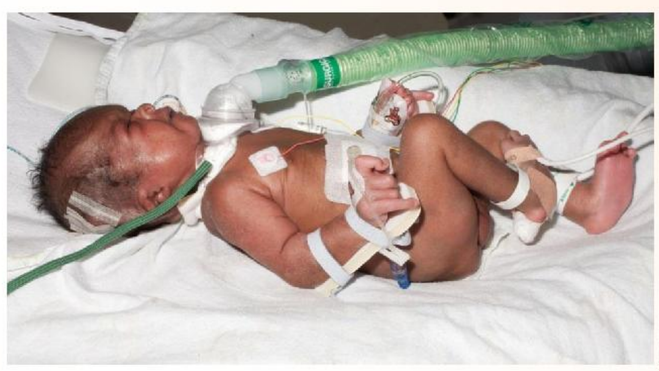
- **Second child of non-consanguinous parents**, **BW=2.7kg (-0.95 SDS), OFC=34,5cm**
- **Facial features**: abnormal scalp shape with very large anterior fontanelle, **midface hypoplasia**; flat nasal bridge, **proptosis/exorbitism**; **small ears** with thickened helices and **absent auditory meatus**;
- ***Neurosurgery d2 – 4:*** **lumbo-sacral myelomeningocoele** – closure d2, **Arnold Chiari malformation**, **ventriculomegaly** – right VP shunt placement d4 (later revised), **craniosynostosis**;
- **Mild stenosis right main bronchus** on bronchogram;
- **Skeletal dysplasia**: **arachnodactyly**, postural **scoliosis**, **rocker-bottom feet, bilateral talipes**;
- **Ambiguous genitalia**: **female external genitalia, palpable labial testicles**;
- **Other problems**: **myoclonic jerks**, **small PFO**, **NG fed →PEG fed**, **mucous rectal prolapse**;
- **Raised as a girl** and **gonadectomy performed at 11 months of age**;
- **Her younger sister was healthy and unaffected.**

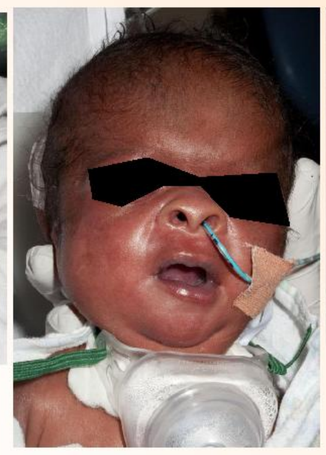
Methods

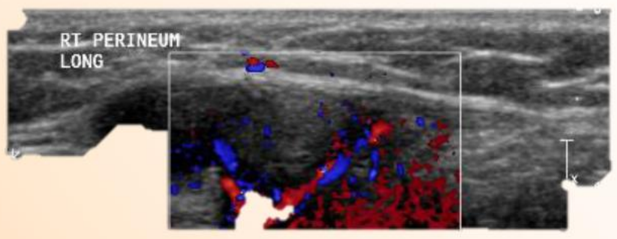
Ultrasound scan (USS) survey (brain, pelvic) :

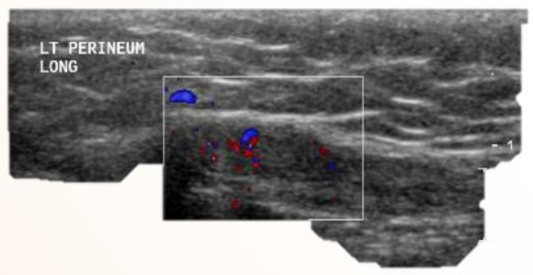




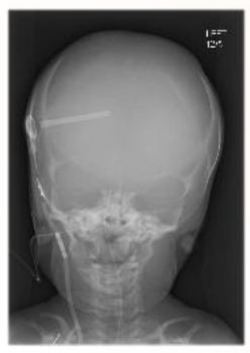


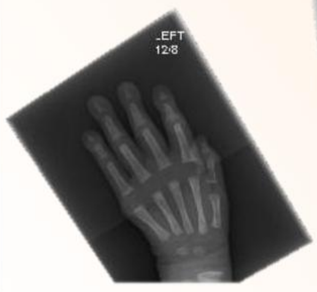


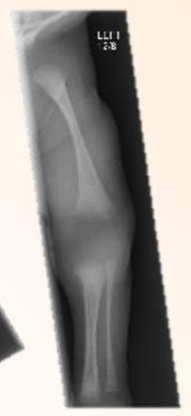




Skeletal survey:







Karyotype: 46, XY

Hormonal analyses:

- **A short synacthen test (SST)** - adrenal insufficiency and the patient was started on hydrocortisone replacement.
  (17OHP was 20.6 nmol/L).

Urinary steroid profiling by gas chromatography mass-spectrometry (GC/MS):

- showed **combined 21-hydroxylase and 17alpha-hydroxylase/17,20 lyase deficiency**, indicative of PORD.

Molecular genetic analysis of the *POR* gene:

- compound heterozygosity for a novel missense mutation p.A200T;
- novel intronic c.1248+1G>T mutation, predicted to cause aberrant mRNA splicing.

	Allele 1	Allele 2	Reference sequence
Genomic	g.27137G>A (exon 5)	g.30967G>T (intron 10)	NG_008930
cDNA	c.598G>A	c.1248+1G>T	NM_000941
Protein	p.Ala200Thr		NP_0000932

Discussion

- **Cytochrome P450 oxidoreductase** - flavoprotein that donates electrons to all microsomal P450 enzymes, including the steroidogenic enzymes P450c17 (CYP17A1; 609300), P450c21 (CYP21A2; 613815), and CYP51A1 (601637) [1].
- The human ***POR*** (OMIM *147370) **gene** maps to chromosome band 7q11.2: from base pairs 75,915,102 to 75,986,855 (71,754bp) [1].
- **Antley-Bixler Syndrome (POR Deficiency) is an extremely rare disorder with impaired steroidogenesis and skeletal anomalies and evidence of homozygous or compound heterozygous mutations in the gene encoding cytochrome P450 oxidoreductase (*POR*; 124015) on chromosome 7q11.2** [2];
- **Autosomal recessive** inheritance;
- **Mortality of 80% at neonatal period** due to airway compromise **and decreases with increasing age** [3];
- **Overlap phenotype**: ***POR*** **or *FGFR2* gene mutations will distinguish the entity** [4, 5];
- **More frequent occurrence of genital abnormalities in females with impaired steroidogenesis and AB Syndrome** [6];
- **Treatment of manifestations**;
- **Prevention of secondary complications** - 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 DSD indicated PORD.

GC/MS analysis reliably detects PORD in affected children and can help with prenatal diagnosis in further pregnancies. Assessment of adrenal function should be part of the early investigations in complex DSD.

References

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