Case Report
doi: 10.4183/aeb.2012.479

A CASE OF ANTLEY BIXLER SYNDROME: DIAGNOSIS AND OUTCOME

M. Puiu[1,2], C. Pienar*[1,2], A. Chirita Emandi[1,2], S. Arghirescu[1,2], C. Popa[1,2], I. Micle[2]

1."Victor Babes" University of Medicine and Pharmacy, 2"Louis Turcanu" Emergency Hospital for Children, Timisoara, Romania

Abstract

Introduction. The Antley-Bixler syndrome (ABS) is an extremely rare syndrome characterized by congenital craniosynostosis and radiohumeral synostosis. Many patients demonstrate defects in steroidogenesis and disturbances of sexual development.

Aim: To present the first documented case of a Romanian patient with ABS.

Material and Methods. Alexandru, a 3 year old child, was referred to our department for elucidating a complex malformative syndrome that consisted of ambiguous genitalia and skeletal anomalies. We performed a complete assessment that ranged from obtaining a detailed medical history to gene sequencing.

The hospital's Ethical Committy gave the authors its approval for using the medical data concerning the case, after the parents signed an informed consent.

Results. *Medical history.* We note 4 previous admissions to our hospital during which efforts were made to diagnose the child's disorder of sexual development. At 3 months Edwards syndrome was suspected, which was later infirmed. During the third and fourth admission (8 months, 10 months respectively) the suspicion of congenital adrenal hyperplasia (CAH) was raised and then confirmed (impaired steroidogenesis, 46 XX karyotype). The patient was lost to follow-up since then, probably due to the parents' inability to cope with the implications of their child's condition.

CASE REPORT

The patient was born to healthy young parents: 19 years old mother and 23 years old father that came from a rural setting. Both parents deny consanguinity and the presence of congenital anomalies in their families. The mother presented with virilization during pregnancy: hirsutism and deepening of the voice. The child, Gesta: 1 Para: 1, was born at 35 week small for gestational age with a weight of 1.85 kg (below the 10th percentile according to Fenton, 2003), a height of 44 cm and a head circumference of 30 cm with an Apgar score of 7. The parents registered the child as a male and

*Correspondence to: Corina Pienar, MD."Louis Turcanu" Emergency Hospital for Children, Iosif Nemoianu Nr. 2-3 Timisoara 300011 Romania. Email:cpienar@gmail.com

raised him gender appropriately.

Physical assessment. At admission, the anthropometric measurements revealed a weight of 10 kg (-2.85 SDS) and a height of 91 cm (-1.38 SDS) using WHO Growth Standards.

The overall appearance was particular. The facial anomalies consisted of: brachycephaly, frontal bossing, midface hypoplasia, depressed nasal bridge, prolonged nasal philtrum, proptosis, anterior and low set years (Fig. 1). We also noted: bilateral elbow synostosis, arachnodactyly and digital clubbing (Fig. 2). The external genitalia was consistent with stage III/IV on the Prader scale (Fig. 3): clitoromegaly, fused labia, single urogenital orifice. The physical exam was otherwise unremarkable.

Blood work-up. Serum electrolytes were in normal range. The hormonal profile revealed a high 17 OH progesterone level, while DHEAS, cortisol, testosterone, LH and FSH were in normal range.

We also repeated the karyotype which was 46 XX 21ss, 22ss. Blood samples of the child and parents were sent to Freiburg University where the POR gene was sequenced. The A287P mutation was found, which consists of a

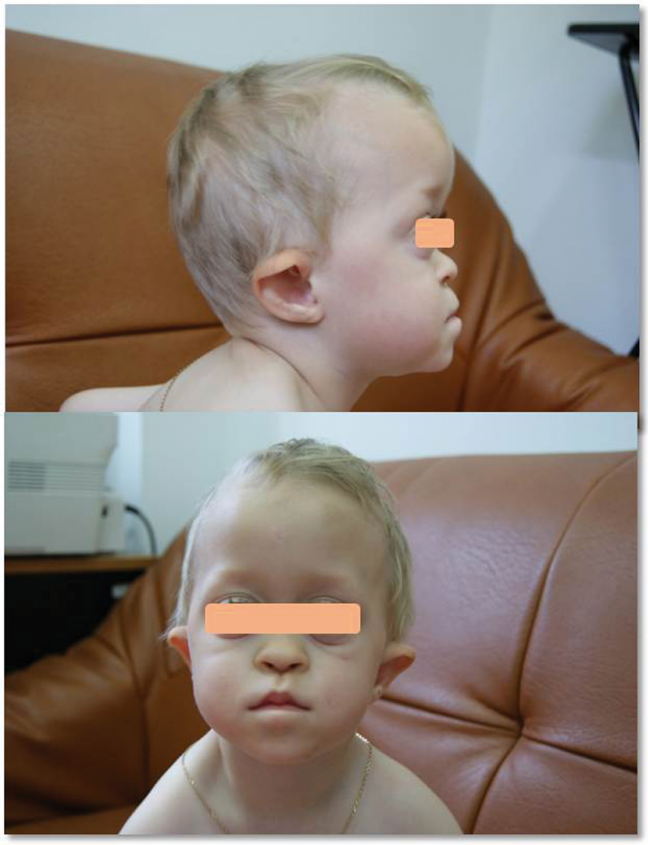

Figure 1. Case ABS. Facial anomalies

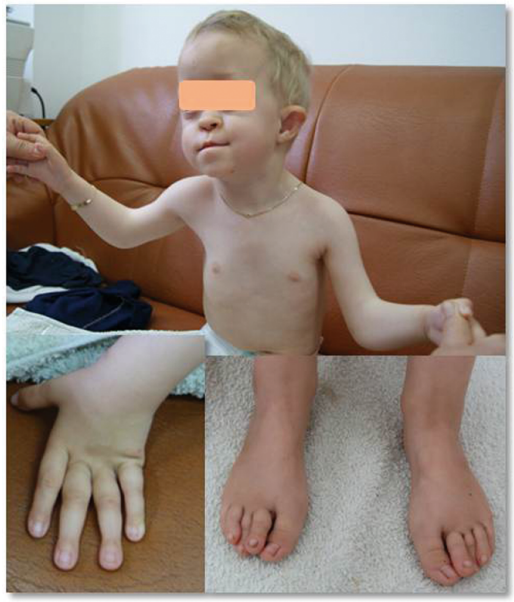

Figure 2. Case ABS. Bilateral elbow synostosis, arachnodactyly and digital clubbing

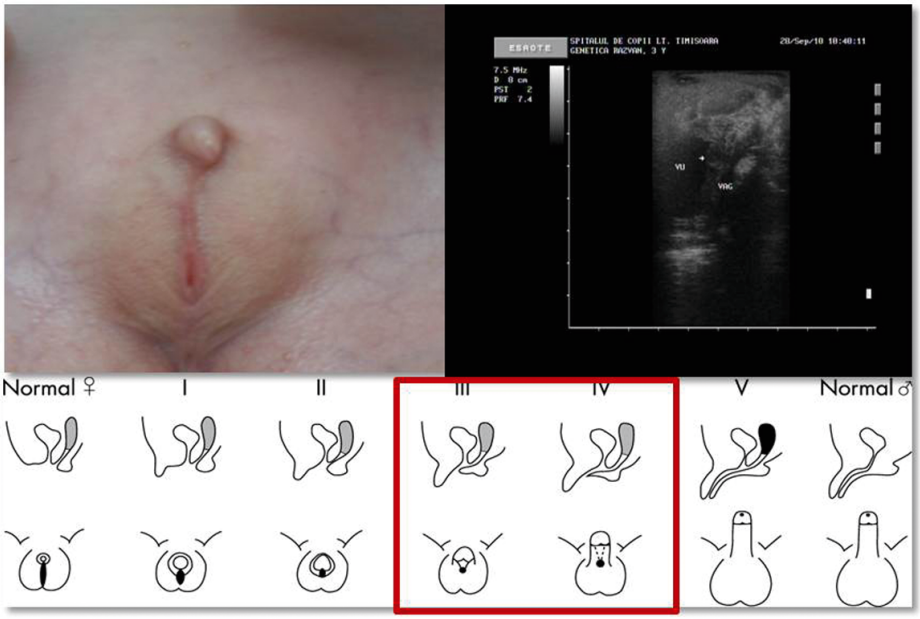

Figure 3. Case ABS. The external genitalia stage III/IV Prader scale

homozygous transversion c.859G→C. Each parent was found to be carrying the transversion in the heterozygous state.

Imaging studies. X-rays of the limbs and cranium revealed bilateral carpal and elbow synostosis and brachycephaly, respectively. The heart ultrasound found an ostium secundum atrial septal defect; the abdominal ultrasound was unremarkable, while the perineal ultrasound confirmed the urogenital sinus and the presence of the uterus (Fig. 3).

Consults. The ophthalmologist confirmed the proptosis. The neurologist found a mild psycho motor delay and speech difficulties. The otolaryngology consult did not find an auditory impairment.

Diagnosis. The clinical suspicion-ambiguous genitalia associated with bones' anomalies, sustained by blood work-up and imaging studies and later confirmed by gene sequencing established the diagnosis of Antley Bixler syndrome with ambiguous genitalia and impaired steroidogenesis.

DISCUSSION

It's highly debated presence in the family of king Tutankhamun entitles Antley-Bixler syndrome to a 5000 years history (3,4). It was first described in 1975, when Antley and Bixler described a patient with trapezoidocephaly, midfacial hypoplasia and cartilage abnormalities with multiple synostoses and skeletal fractures. Since then more than 50 cases were published. In 1997, Crisponi *et al.* suggested that about half of the cases described as Antley-Bixler syndrome had impaired steroidogenesis.

ABS spectrum. In addition to a wide spectrum of anomalies, ABS is also genetically heterogeneous with at least two distinct disorders, (1) ABS without disordered steroidogenesis, a variant of the autosomal dominant fibroblast growth factor receptor (FGFR)–related craniosynostosis syndromes (MIM 2017410), and (2) ABS with disordered steroidogenesis, caused by several mutations in the gene encoding cytochrome P450 oxidoreductase (POR) (MIM 201750) (5–7).

POR: the link between impaired steroidogenesis and bones' anomalies. POR serves as the electron transporter for cytochrome P450 enzymes, including those involved in steroidogenesis: 17-hydroxylase, 21-hydroxylase and aromatase(2,8,9). Its deficiency (MIM 613571) results in a rare variant of congenital adrenal hyperplasia, an apparent combined deficiency of 17-hydroxylase and 21-hydroxylase. Furthermore, cytochrome P450 enzymes are involved in the metabolism of cholesterol (2,8). In the mouse model it has been shown that cellular POR-dependent cholesterol synthesis is essential during limb and skeletal development (10).

The POR gene. The human POR gene, encoding a P450 oxidoreductase, is located at 7q11.2 and contains 15 coding exons. The A287P mutation is a frequent mutation causing POR deficiency in Caucasians (5,11), while the R457H is strongly-but not uniquely-associated with patients of Japanese heritage. The A287P mutation consists of a nucleotide change 859G/C. This mutation was also found in our patient

in a homozygous state. The resulting polypeptide shows a 60-80% reduction of enzymatic activity compared to the wild type enzyme (8).

Outcome of our patient. As far as we know, our patient is the first Romanian case of Antley-Bixler syndrome confirmed through gene sequencing.

Our patient did not require continuous steroid supplementation, but we informed the parents that the substitution might be necessary in case of illness or surgery. We recommended physical therapy for the elbow synostosis and speech therapy. The family received genetic and psychological counseling.

The most pressing matter for the parents was the ambiguous genitalia. Life in a small rural community and low educational level made it difficult for the family to cope with the child's condition. In the end, the multidisciplinary team succeeded in making them understand the complex nature of their child "illness". After being informed about the risks and benefits of the procedures, the parents opted for corrective clitoroplasty and vaginoplasty.

After the surgery, the child was legally registered and raised as a girl-Alexandra and she remains in close follow-up. While the short term outcome is good, the long-term outcome is uncertain because of the hormonal imprinting of the brain, which may lead to psychological problems in adolescence and adult life.

In conclusion, Alexandra is the first Romanian patient with Antley-Bixler syndrome confirmed through gene sequencing. She requires close and multidisciplinary follow-up. While the most pressing matter for the parents- the ambiguous genitalia- was resolved and the short term outcome is favorable, on the long run psychological problems may appear.

Acknowledgements. We would like to express our gratitude to the Freiburg University Hospital team, especially Ekkehart Lausch, who made possiblethe POR gene sequencing.

Conflict of interest.

The authors did not report any conflict of interest.

References

1.McGlaughlin KL, Witherow H, Dunaway DJ, David DJ, Anderson PJ. Spectrum of Antley-Bixler syndrome. J Craniofac Surg. 2010;21(5):1560–1564.

2.Porter FD, Herman GE. Malformation syndromes caused by disorders of cholesterol synthesis. J Lipid Res [Internet]. 2010,7 [cited 2010 Oct 19]; Available at: http://www.ncbi.nlm.nih.gov/pubmed/20929975

3.Hawass Z, Gad YZ, Ismail S, Khairat R, Fathalla D, Hasan N, et al. Ancestry and pathology in King Tutankhamun's family. JAMA. 2010;303(7):638–647.

4.Braverman IM, Redford DB, Mackowiak PA. Akhenaten and the strange physiques of Egypt's 18th dynasty. Ann. Intern. Med. 2009;150(8):556–560.

5.Herkert JC, Blaauwwiekel EE, Hoek A, Veenstra-Knol HE, Kema IP, Arlt W, et al. A rare cause of congenital adrenal hyperplasia: Antley-Bixler syndrome due to POR deficiency. Neth J Med. 2011;69(6): 281–283.

6.Raducanu-Lichirdopol C. Male Pseudohermaphroditism Caused by an Inborn Error in Cholesterol Biosynthesis: Smith-Lemli-Opitz Syndrome. Acta Endocrinol (Buc). 2006; 2(3):365–75.
7.Cragun D, Hopkin RJ. Use of the term "Antley-Bixler syndrome": minimizing confusion. Am. J. Hum. Genet. 2005 Aug;77(2):327–328; author reply 328–340.
8.Miller WL. Minireview: regulation of steroidogenesis by electron transfer. Endocrinology. 2005;146(6):2544–2550.
9.Pandey AV, Kempná P, Hofer G, Mullis PE, Flück CE. Modulation of human CYP19A1 activity by mutant NADPH P450 oxidoreductase. Mol. Endocrinol. 2007; 21 (10):2579–2595.
10.Schmidt K, Hughes C, Chudek JA, Goodyear SR, Aspden RM, Talbot R, et al. Cholesterol metabolism: the main pathway acting downstream of cytochrome P450 oxidoreductase in skeletal development of the limb. Mol. Cell. Biol. 2009;29(10): 2716–2729.
11.Huang N, Pandey AV, Agrawal V, Reardon W, Lapunzina PD, Mowat D, et al. Diversity and function of mutations in p450 oxidoreductase in patients with Antley-Bixler syndrome and disordered steroidogenesis. Am. J. Hum. Genet. 2005; 76(5):729–749.