*British Journal of Medicine & Medical Research*
*14(10): 1-4, 2016, Article no.BJMMR.24651*
*ISSN: 2231-0614, NLM ID: 101570965*

**SCIENCEDOMAIN** *international*
www.sciencedomain.org

# A Case of Antley-Bixler Syndrome with New Genetic Study Result

**Zohreh Karamizadeh[1], Hamdollah Karamifar[1], Gholamhossein Amirhakimi[1], Hossein Moravej[1*] and Ladan Nasermoaddeli[2]**

*[1]Department of Pediatric, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.*
*[2]School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.*

***Authors' contributions***

*This work was carried out in collaboration between all authors. Author ZK designed the study and wrote the protocol. Authors HK and GA managed the literature searches. Author HM collected the data and wrote the first draft of the manuscript. Author LN managed the literature searches and wrote the draft of the manuscript. All authors read and approved the final manuscript.*

***Article Information***

DOI: 10.9734/BJMMR/2016/24651
Editor(s):
(1) Mohammed Rachidi, Molecular Genetics of Human Diseases, French Polynesia, University Paris 7 Denis Diderot, Paris, France.
(2) Valeria Denninghoff, Molecular Pathology and Molecular Onco-Hematology laboratory, University Institute CEMIC, Argentina.
Reviewers:
(1) Satesh Bidaisee, St. George's University, Grenada.
(2) Jerzy Bełtowski, Medical University, Lublin, Poland.
(3) Ali Al Kaissi, Ludwig Boltzmann Institute of Osteology, Vienna, Austria.
Complete Peer review History: http://sciencedomain.org/review-history/13959

***Case Study***

***Received 28th January 2016***
***Accepted 16th March 2016***
***Published 31st March 2016***

## ABSTRACT

**Aims:** Antley-Bixler syndrome (ABS) is a rare disease which is a complex of skeletal, visceral, extremity and genital anomalies and occasionally is associated with adrenal insufficiency due to P450-oxidoreductase deficiency.
In this article we report a patient, a suspicious case of ABS with different phenotypic and genotypic characteristics.
**Presentation of Case:** The patient is a male infant with facial dysmorphism, syndactyly, multiple joint contractures, and ambiguous genitalia.
He had hyponatremia, hyperkalemia and elevated 17.OH.progestrone level of serum. In genetic analysis, no mutation was found in POR gene.
**Discussion:** This patient has clinical and paraclinilical manifestations of ABS. Although different mutations have been reported as the cause of this syndrome, all reported patients who suffered

**Corresponding author: E-mail: hmoravej@sums.ac.ir;*

from adrenal insufficiencies, had mutations in POR gene.
**Conclusion:** According to our search in literature, this is the first case of ABS associated with adrenal insufficiency who does not have any mutation in POR gene.
More genetic studies are needed to determine new mutations in such patients.

*Keywords: Antley-Bixler; P450 oxidoreductase deficiency; congenital adrenal hyperplasia; ambiguous genitalia.*

## 1. INTRODUCTION

Accompaniment of congenital adrenal hyperplasia with somatic symptoms has been detected in a rare disease, called Antley-Bixler Syndrome (ABS). This syndrome is a complex of some skeletal, facial, visceral and extremity anomalies that occasionally is associated with P450-oxidoreductase (POR) deficiency [1].

This syndrome has both autosomal recessive and autosomal dominant inheritance [2].

Although different mutations have been reported in ABS, patients with ambiguous genitalia have mutations in POR gene, but patients without abnormality in urogenital system may have mutations in different genes [3,4].

In this article, we report the first patient with clinical features of ABS, but without mutation in POR gene.

## 2. PRESENTATION OF CASE

The patient is a boy, born to a middle-aged multigravida mother. He presented in neonatal period with vomiting, severe dehydration and lethargy as a case of adrenal crisis. Other clinical manifestations of this case were as below:

**Head and neck:** Depressed nasal bridge, low set anterior hairline, dysphonia, bulged anterior fontanels, choanal stenosis.

**Extremities:** Contracture of both elbows, overriding of second and third fingers of hands, comptodactyly, syndactyly of fingers of both feet, multiple joint contractures.

**Genitalia:** Micropenis, bilateral undescended testes, labioscrotal fusion.

Figs. 1 and 2 show some facial and skeletal features of the patient.

The patient did not have some other manifestation of ABS such as: Craniosynostosis and mid-face deformities.

The parents are not relatives and they do not have any significant family history.

**Fig. 1. Facial feature of the patient; depressed nasal bridge is clear in this picture**

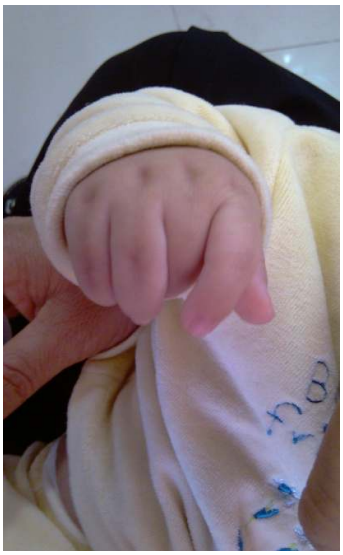

**Fig. 2. Overriding of 2nd and 3rd fingers of the hand**

In laboratory studies, he had hyponatremia and hyperkalemia and his 17 OH progesterone level

was increased. Blood Urea Nitrogen and creatinine were normal. Steroid therapy started for him as a case of congenital adrenal hyperplasia and continued with oral hydrocortisone and fludrocortisone.

**Abdominal sonograghy:** Moderate hydronephrosis in left kidney, mild calyceal and moderate pelvic dilatation in left kidney.

Brain sonography due to bulged fontanels: Mild dilatation of lateral and third ventricles.

**Echocardiography:** Septal hypertrophy, early diastolic dysfunction.

POR sequencing research testing was done for the patient. All coding exons were sequenced and no pathologic mutation was identified.

This genetic study was performed in Dr.Ethylin Wang Job's laboratory, USA.

Now, the patient is a 2 years old boy. His dysphonia improves. He is on treatment with Hydrocortisone and fludrocortisone and has received a regimen of 3 month intramuscular testosterone as a treatment for micro-penis with good response. He has had only one episode of adrenal crisis in 7 month of age.

Informed consent was taken from parents of the patient before publication of this case report.

## 3. DISCUSSION AND CONCLUSION

Anthley and Bixler in 1975 presented the first case of ABS with midfacial defects, bowing of femors, humeroradial synostosis and other abnormalities [5]. So far about 50 cases have been reported [6].

Chilinical manifestation of ABS include: Midface hapoplasia, craniosynostosis, choanal atresia or stenosis, femoral bowing, multisynostotic osteodysgenesis, multiple joint contractures, neonatal fractures, and occasionally urogenital anomalies [7].

Mortality of ABS in neonatal period is about 80%, but the prognosis improves with increasing age [2].

Some of them need physical therapy to capture normal functional abilities [3].

Our patient had Hyponatremia, hyperkalemia and increase in 17 OH Progesterone. Certainly, he is a case of congenital adrenal hyperplasia (CAH).

The patient has also some of the manifestations of ABS such as: Depressed nasal bridge, low set anterior hairline, choanal stenosis, contracture of the elbows, syndactyly, multiple joint contractures, but he doesn't have some other symptoms of ABS. Some cases of ABS have normal genitalia and normal adrenal function, but all the ABS patients associated with ambiguous genitalia have CAH due to P450-Oxidoreductase deficiency. On the other hand, mutation in POR gene is found in some cases of CAH without skeletal deformities of ABS.

So far, all ABS patients who have had ambiguous genitalia, had mutations in POR gene. POR gene encodes a flavoprotein which facilitates electron transfer from NADPH to cytochrome P450 enzymes including CYP19A, VYP 21A2 and CYP 17 A1 [8]. Herkert et al reported a teenaged girl with menstrual problems, dysmophic face and adrenal insufficiency. She had a missence mutation in POR gene [8]. The first reported ABS patient from Hong Kong presented in 4 years of age with adrenal crisis [9]. Guaragna-Filho et al reported a case of POR deficiency with ABS who did not show skeletal manifestations in infancy. His osteoarticular abnormalities were detected first in 7 years of age. It indicates that all POR deficient patients should be examined periodically to detect possible skeletal problems [10]. According to our search in literature, our patient is the first reported case who has combination of CAH, ambiguous genitalia and skeletal and somatic abnormalities but no pathologic mutation in POR gene was found.

In conclusion, this case can be the first case of ABS with ambiguous genitalia that has mutation in genes other than POR or he can be a new syndrome which has not been reported yet. More extensive genetic studies on the patients with CAH will help the diagnosis.

## ETHICAL APPROVAL

This study is approved by Ethical Committee of Shiraz University of Medical Sciences.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Jung Min Ko, Chong-Kun Cheon, Gu-Hwan Kim, Han-Wook Yoo. A case of Antley-Bixler syndrome caused by compound heterozygous mutations of the cytochrome P450-oxidoreductase gene. Eur J Pediatr. 2009;168:877-880.
2. Lahiri S, Ghoshal B, Nandi D. A case of Antley-Bixler syndrome. J Clin Neonatol. 2012;1(1):46-8.
   DOI: 10.4103/2249-4847.92232
3. Del Rossi L. Gross motor function of a child with Antley-Bixler syndrome. Pediatr Phys Ther. 2015;27(4):452-9.
   DOI: 10.1097/PEP.0000000000000176
4. McGlaughlin KL, Witherow H, Dunaway DJ, David DJ, Anderson PJ. Spectrume of Antley-Bixler syndrome. Journal of Craniofacial Surgery. 2010; 21(5):1560-4.
5. Antley R, Bixler D. Trapezoidocephaly, midface hypoplasia and cartilage abnormalities with multiple synostoses and skeletal fractures. Birth Defects Orig Artic Ser. 1975;11:397–401.
6. Jones KL. Smith's recognizable patterns of human malformation. 6th ed. Noida: Elsevier, Craniosynostosis Syndromes. 2006;488–91.
7. Lee H-J, Cho D-Y, Tsai F-j, Shen W-C. Antley-Bixler syndrome, description of two new cases and review of the literature. Pediatr Neurosurg. 2001;34:33-39.
   DOI: 10.1159/000055989
8. Herkert JC, Blaauwwiekel EE, Hoek A, Veenstra-Knol HE, Kema IP, Arlt W, Kerstens MN. A rare cause of congenital adrenal hyperplasia: Antley-Bixler syndrome due to POR deficiency. Neth J Med. 2011;69(6):281-3.
9. But WM, Lo IF, Shek CC, Tse WY, Lam ST. Ambiguous genitalia, impaired steroidogenesis, and Antley-Bixler syndrome in a patient with P450 oxidoreductase deficiency. Hong Kong Med J. 2010;16(1):59-62.
10. Guaragna-Filho G, Castro CC, Carvalho RR, Coeli FB, Ferraz LF, Petroli RJ, Mello MP, Sewaybricker LE, Lemos-Marini SH, D'Souza-Li LF, Miranda ML, Maciel-Guerra AT, Guerra-Junior G. 46,XX DSD and Antley-Bixler syndrome due to novel mutations in the cytochrome P450 oxidoreductase gene. Arq Bras Endocrinol Metabol. 2012;56(8):578-85.




*Peer-review history:*
*The peer review history for this paper can be accessed here:*
*http://sciencedomain.org/review-history/13959*